Assessment of the value of

LAMOTRIGINE

in daily practice

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Een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

PROEFSCHRIFT

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Introduction

OBJECTIVES OF THE THESIS

The recurring theme of this thesis is the assessment in daily practice (i.e. after approval) of the value of lamotrigine, a relatively new drug in the treatment of epilepsy. The case of lamotrigine illustrates the need for effectiveness data in addition to the efficacy data obtained in randomised clinical trials. In addition, lamotrigine was the first drug in the Netherlands for which a prescription guideline aiming at cost containment was applied.

The main objectives of this thesis are to gain insight in:
- the positioning of new antiepileptic drugs;
- the outcomes in patients using lamotrigine;
- clinical and health policy decision making.

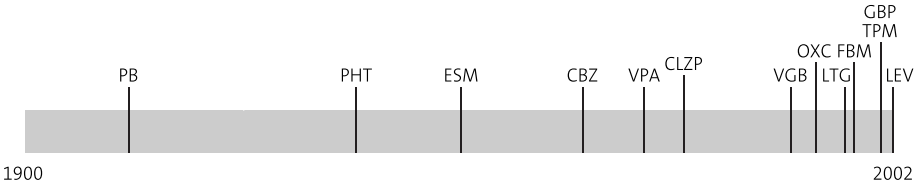
Research principles and methods from pharmacoepidemiology and pharmaco–economics will be applied to attain these objectives. The remainder of this introductory chapter provides information on epilepsy and its drug treatment, the learn–confirm cycle of drug evaluation and the differences between randomised controlled trials and observational studies. At the end of this chapter the outline of the thesis is given.

EPILEPSY

Epilepsy is a neurological disorder characterised by recurrent, unprovoked seizures (1). Epilepsy is not a uniform condition, but comprises many different seizure types and epilepsy syndromes. An epileptic seizure is the clinical manifestation of an abnormal and excessive synchronised discharge of a set of cerebral neurones (2). These clinical manifestations are sudden and transient and can include a wide variety of movement, feeling or psychic disturbances, with or without alteration in consciousness. Seizures are broadly divided into two categories: partial and generalised. Partial seizures arise in a so–called epileptogenic region in one hemisphere of the cerebral cortex. They are subdivided into simple partial seizures, which occur without alteration of consciousness, and complex partial seizures, in which consciousness is impaired or lost. These seizures may generalise into a secondary generalised tonic clonic seizure. Primary generalised seizures are characterised by more diffuse neuronal discharges involving both hemispheres of the brain at once and always result in loss of consciousness.

Epilepsy is one of the most common neurological disorders. The prevalence is around 0.5% – 1%; it is assumed that there are about 100,000 individuals with epilepsy in the Netherlands (3). The incidence in industrialised countries has been estimated to be around 50 cases per 100,000 persons per annum (range 40 – 70/100,000 people per annum) (3,4). The incidence varies greatly with age with peak rates occurring in early

Figure 1. Approval dates of antiepileptic drugs in the Netherlands



PB: phenobarbital. PHT: phenytoin. ESM: ethosuximide. CBZ: carbamazepine. VPA: valproate. CLZP: clonazepam. VGB: vigabatrin. OXC: oxcarbazepine. LTG: lamotrigine. FBM: felbamate. TPM: topiramate. GBP: gabapentin. LEV: levetiracetam

childhood and in those aged over 65. Epilepsy has a great impact on patients' lives. Restrictions of work or schooling are among the most frequently stated impacts in all age groups and severity groups (5). In adults, driving restrictions were also frequently stated as a far–reaching consequence. People with epilepsy are more often unemployed and experience limited choice and advancement in the workplace. It has been found that the quality of life, particularly in psychological and psychosocial domains, is markedly diminished in patients with active epilepsy, which may be partly drug–induced (5).

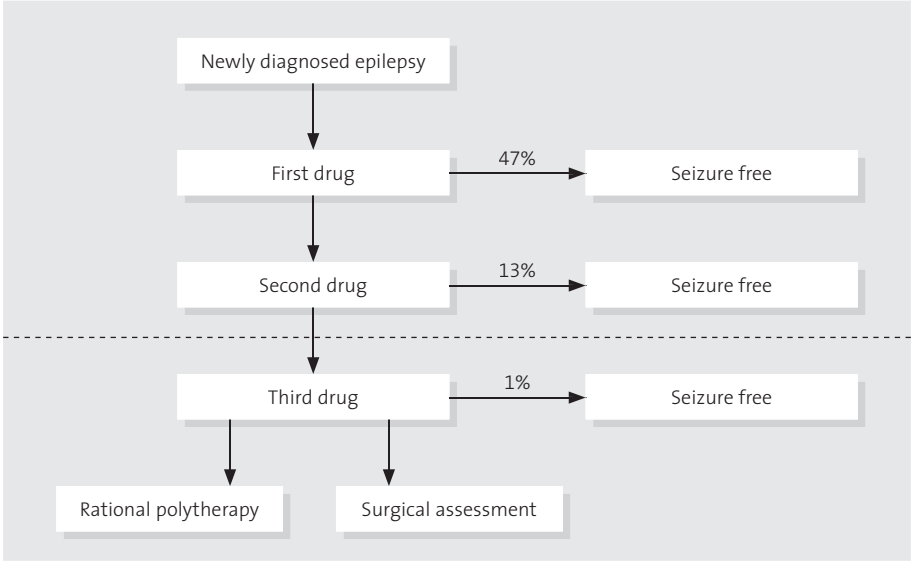
GENERAL PRINCIPLES OF TREATMENT

Drug therapy is the mainstay of epilepsy management, although resective surgery has become a realistic option for patients with certain types of difficult–to–treat epilepsy. The field of antiepileptic drug therapy has been an unusual one, being dominated for decennia by older drugs such as carbamazepine, phenobarbital, phenytoin and valproate (figure 1) (6). Several limitations of these conventional antiepileptic drugs restrict their use. First, the adverse effects of these antiepileptic drugs are troublesome. Monotherapy trials show that a majority of patients can expect to experience adverse effects related to their medication (7,8). These adverse effects may vary from mild feelings of fatigue to life–threatening hypersensitivity reactions.

Second, some of the conventional antiepileptic drugs have complex pharmacokinetic properties and considerable potential for drug interactions with numerous other drugs. A third limitation of the conventional antiepileptic drugs is that they are associated with an increased risk for major foetal malformations

The decision to initiate drug therapy therefore depends on a difficult–to–define balance between the likelihood of further seizures versus the possible drawbacks of therapy (9). The aim of treatment is to abolish seizures completely, while keeping the adverse effects of treatment to a minimum. Treatment with a single drug is generally

Figure 2. Staged approach to epilepsy management

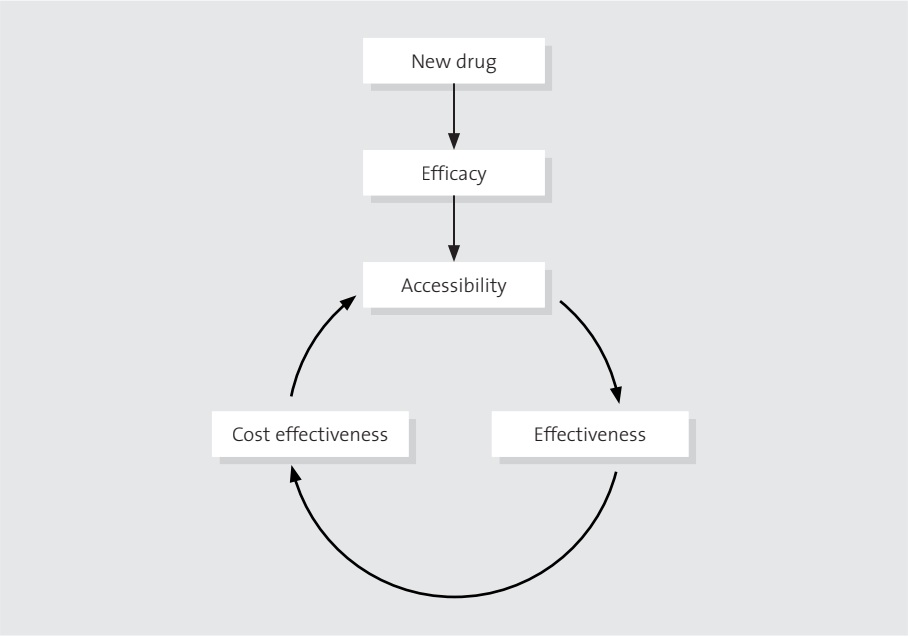


Adapted from Kwan et al. (10).

preferred, because monotherapy is associated with less–intrusive regimens, better tolerability and absence of interactions with other antiepileptic drugs. Monotherapy is initiated by gradually increasing the dose until seizures are controlled or adverse effects become unacceptable.

The outcome of therapy in newly–diagnosed patients with epilepsy is reasonably good. Around 60% of new epilepsy patients will be satisfactorily controlled with the first or second antiepileptic drug (figure 2) (10). The most powerful predictor of refractory epilepsy is response to the first or first two antiepileptic drugs. This supports the hypothesis that patients with newly–diagnosed epilepsy comprise two distinct populations. The aforementioned 60 to 70% have a good prognosis, and become seizure free on a modest dose of the first– or second–line antiepileptic drug without developing intolerable adverse effects. The remaining 30 to 40% of the patients have refractory epilepsy and despite combination therapy will not become seizure free (11,12). The aim of therapy for these patients should be a balance between seizure control and an optimal quality of life. With over ten different antiepileptic drugs currently available, there are more than 80 possible two– and three–drug combinations. A point of criticism on current practice has been that most of the combinations used are based on empirical decisions rather than on rational choices (13). Recently, however, more information on rational polytherapy has become available (11).

Figure 3. Learning-cycle in drug development

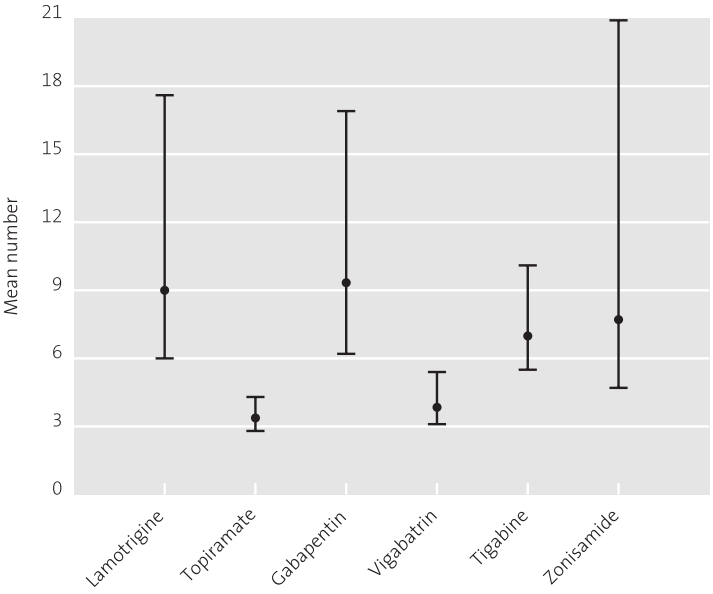


Adapted from Pronk et al. (14).

NEW ANTIEPILEPTIC DRUGS

A number of new antiepileptic drugs has become available in the Netherlands from 1990 onwards (figure 1). In the comparative trials to date, the newer drugs have not yet demonstrated better efficacy compared to conventional drugs, but the newer drugs are claimed to lead to a better quality of life. This improvement has been attributed to various factors, but mainly to more acceptable adverse effect profiles. It is likely that there will be a substantial market for any antiepileptic drug that has proven to address the limitations of the conventional antiepileptic drugs. The acquisition cost of the new antiepileptic drugs are, however, a factor 5 – 20 higher than that of the older generation of drugs. Because epilepsy represents one of the most common neurologic disorders, an indiscriminate switching from old to new antiepileptic drugs would have considerable health economic implications (6). The crucial issue for new antiepileptic drugs is, however, not their cost, but their cost–effectiveness. Rational drug use taking cost into account can be seen as the end phase of the learn–confirm cycle of drug evaluation (figure 3). Evaluation can be achieved in four successive steps; efficacy, accessibility, effectiveness and cost–effectiveness. In each step both therapeutic and financial aspects are taken into account, the different steps are addressed below (14).

Figure 4. Efficacy of new antiepileptic drugs



Mean (95% confidence interval) number needed to treat to get one responder (defined as a patient with at least 50% seizure reduction) with each of six drugs. Adopted from Marson et al. (17) and Elferink et al. (40).

EFFICACY OF NEW ANTIEPILEPTIC DRUGS

The Netherlands has a strict programme for the evaluation of new drugs (15). The registration authority requires proof of efficacy and safety before the drug can be introduced to the market. It is an established fact that evidence for demonstrating efficacy can best be obtained through randomised controlled trials, in which eligible patients are randomly assigned to either a group using the new drug or to a comparison group (16). New antiepileptic drugs receive regulatory approval as a result of placebo–controlled, add–on randomised controlled trials, in patients with refractory epilepsy. The primary efficacy parameter is usually a 50% or more reduction in seizure frequency in the trial period, compared to the baseline seizure frequency. Attempts have been made to provide a comprehensive systematic quantitative review of antiepileptic drug efficacy by combining the results of all available data from the placebo–controlled clinical trials (17,18). These meta–analyses showed a trend towards a better efficacy with drugs such as topiramate and vigabatrin than with drugs such as gabapentin and lamotrigine (figure 4). These reviews have been criticised on various counts, and the consensus is that different results would have been obtained if different dosages had been used for the various drugs (2,19).

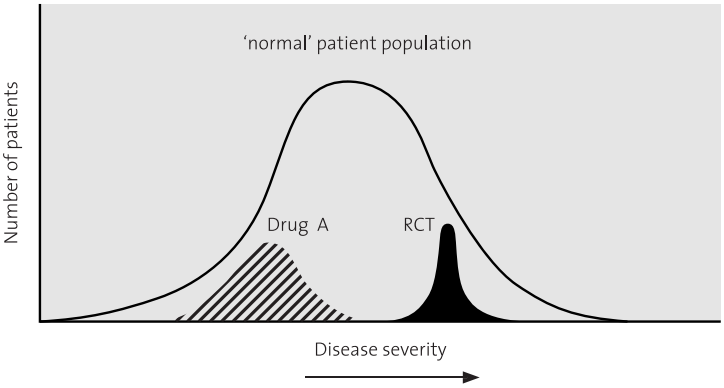
Regulatory approval efficacy studies provide information that only scratches the surface of potentially available information about a new drug (20). Regulatory trials are designed primarily to prove that a drug works (compared to placebo) in patients to whom it is given. These randomised controlled trials typically take place in highly selected populations in standardised situations, in order to make the statistical evaluation of efficacy more efficient (21). Patients with multiple diseases, compliance problems and other complex health problems are often excluded (20,22). Moreover, the regulatory trials of new antiepileptic drugs examine efficacy over a short duration, typically only 3–6 months. It is taken on faith that the effect will not wane over a longer period. Whenever new antiepileptic drugs have reached the market, there have been on average 3,000 patient exposures over several years' duration (20). This limits the amount of safety data available from randomised controlled trials, as detection of rare adverse drug effects requires a longer follow–up of large groups of patients.

ACCESSIBILITY OF NEW ANTIEPILEPTIC DRUGS

In an insurance–based healthcare system, like the Dutch one, crucial to the accessibility of care is the decision made on reimbursement (23). In this stage it is decided whether a regulatory approved drug is included in the benefit package and under which conditions. As far as social health insurance is concerned, in the Netherlands the reimbursement decision is made by the government with an important advisory and implementation role for the Health Care Insurance Board (College voor zorgverzekeringen). Private insurance companies have full autonomy in deciding what to include in their insurance policies. In practice, however, they tend to follow the corresponding packages in the social health insurances.

The case of lamotrigine illustrates that registration and reimbursement decisions have become clearly distinct processes. Market approval was obtained from the Dutch Medicines Evaluation Board in 1995. A reimbursement decision, however, was not taken until almost two years later by the Health Care Insurance Board. The late reimbursement decision was a consequence of the high acquisition cost of lamotrigine and the relative lack of information about actual clinical (added) value at the moment of approval. This deadlock was ended when the Health Care Insurance Board imposed restrictions on the claim made for the drug. These restrictions were included in a prescribing guideline that was subsequently published. The Lamotrigine Prescription Guideline restricted the use of lamotrigine to patients with refractory epilepsy who failed three consecutive drug treatments, i.e. a patient population rather similar to that in the regulatory trials. The Lamotrigine Prescription Guideline was the first prescription guideline in the Netherlands aiming at cost containment and is also used for the antiepileptic drugs introduced after lamotrigine.

Figure 5. Theoretical distribution patient populations



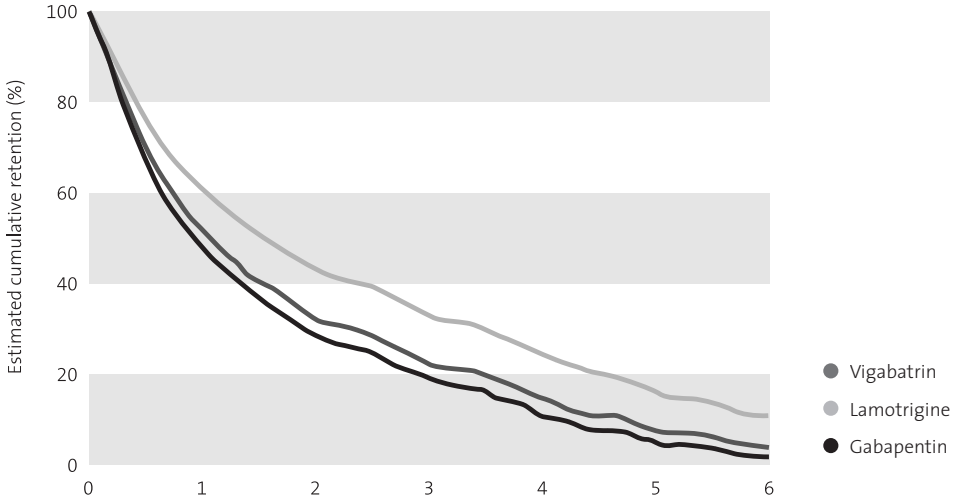
Theoretical distribution of disease severity in a "normal" patient population, in a randomised controlled trial (RCT), and in patients receiving drugs in daily clinical practice (Drug A). Adopted from Leufkens et al. (22).

EFFECTIVENESS OF NEW ANTIEPILEPTIC DRUGS

Effectiveness studies focus on the net benefit of a drug therapy applied in daily clinical practice. Figure 5 shows a prototypical description of the distribution of several patient populations along the dimension of disease severity (22). For regulatory trials of new antiepileptic drugs, patients are recruited who have refractory epilepsy, i.e. patients tend to be positioned at the right side of the figure. Once an antiepileptic drug is on the market and physicians have become familiar with its use and safety, it is often used for patients with less severe epilepsy and for patients excluded from the trials because of age, co-morbidity et cetera (24). Thus, daily clinical practice results in drug exposure to patients from mild to moderate regions of disease severity, as is shown in figure 5. The applicability of trial results to clinical practice is limited, as a result of the large variations in patient characteristics in real life (21,25).

Pharmacoepidemiological research is concerned with the describing and explaining of the dynamics of drug exposure, as well as with the detecting and unravelling of drug-effect relations in large populations. These studies often are observational in nature. Inherent to the non-experimental design of such studies is that the findings are more susceptible to bias than clinical trials and are therefore judged as a lower degree of evidence than trials. For example, if a drug is perceived as highly effective, patients with more severe disease activity may be more likely to receive it. Patients with mild disease activity may be given a drug perceived as "safe". Confounding by indication, due to the non-random assignment, may bias the outcome of observational studies. After their introduction, new antiepileptic drugs have to compete with the drugs already on the market. This can result in selective prescribing of the new drugs, e.g. for patients not

Figure 6. Estimated persistence rate of new antiepileptic drugs in patients with refractory epilepsy



Adopted from Wong et al. (41).

responding to previous therapy or suffering from adverse effects. Selective prescribing, or channelling, may hamper valid observational comparisons between different antiepileptic drugs (26,27). For example, figure 6 appears to suggest that lamotrigine is more effective than gabapentin, when assessed by the cumulative persistence rate. It may well be, however, that the gabapentin group of patients was not comparable to the lamotrigine group with respect to disease severity, due to the fact that both drugs were introduced at two distinctive points in time.

Although observational studies have lower internal validity than randomised controlled trials, they have better external validity as observational studies often represent daily clinical practice patients, whereas trials often include a highly selected study population for a limited period of time. Observational drug evaluation in daily clinical practice is therefore complementary to experimental research. Observational research can offer a clearer picture of the actual value of new antiepileptic drugs in terms of effectiveness and safety. Observational studies with new antiepileptic drugs have shown that the long-term effectiveness in patients with refractory epilepsy was modest. A long-term persistence (i.e. the number of patients that continue drug use) of as low as 15% over six years has been reported in these patients (figure 6) (28–30).

As mentioned above, safety issues are rarely explored within the context of clinical trials. Observational studies with some of the new antiepileptic drugs confirm the need for continued vigilance in this area (31). Vigabatrin, for instance, may cause severe and

irreversible visual–field constriction (32). This case illustrates the differences between efficacy and effectiveness. Vigabatrin was assumed to be relatively highly efficacious, when assessed with pooled short–term randomised controlled trial data (figure 4). However, in long–term observational studies the value of vigabatrin proved to be limited due to insufficient effectiveness and severe adverse events (figure 6).

There is ongoing controversy in medical literature between scientists who adopt the outcome of randomised controlled trials solely, and those who advocate the use of observational studies to evaluate the effectiveness of health care (33–35). Instead of advocates of each approach criticising the other method, an attempt should be made to integrate results from both methods, as they both contribute relevant and complementary information upon which the value of drug therapy can reliably be based.

COST EFFECTIVENESS OF NEW ANTIEPILEPTIC DRUGS

All modern, regulated healthcare environments struggle with such problems as ensuring the quality of care and equity, macro–economic cost control and micro–economic efficiency (36). An area of ongoing concern for policy makers in Western countries is the rapid increase of pharmaceutical expenditures, which is due to factors like ageing of the population and the introduction of new, expensive drugs. In most Western countries pharmaceutical expenditures has reached 10 – 20% of the total healthcare budget. As in many other countries, in the Netherlands there is a growing tension between rising demand for health care and political pressure to contain its costs (23). This tension has led to the insight that new health technologies (e.g. new drugs) should not be incorporated without an evaluation of their added value compared to current standards or acceptable options. This added value must be established in order to gain widespread reimbursement from payers, broad acceptance from providers and patients, and approval from society at large.

The interest in economic evaluations of epilepsy therapy is related to the high prevalence and chronicity of the illness. Economic evaluations involve the comparative assessment of all courses of action in terms of their clinical consequences and resource costs (37). By making all relevant costs and consequences explicit, cost–effectiveness analysis aims to provide information on rational drug use for decision makers on both a macro and a micro level. On a macro level, policy makers like the Health Care Insurance Board has taken the initiative to introduce economic appraisal in the reimbursement procedures (23). On a micro level, information on cost–effectiveness can be very helpful in defining standards or clinical guidelines for good medical practice. Holloway held a survey among a random selection of United States neurologists on the topic of allocating finite resources with an emphasis of decisions on costly drugs (38). Most neurologists

Table 1. Cost-effectiveness of antiepileptic drugs as add-on therapy in patients with refractory epilepsy

Study	Selai 1999 (42)	Messori 1998 (43)	Markowitz 1998 (44)	Hughes 1996 (45)	O'Neill 1995 (46)
Type	Cost-effectiveness	Cost-utility	Cost-effectiveness	Cost-minimisation	Cost-effectiveness
Drugs compared	LTG, TPM	LTG, older AEDs	LTG, older AEDs	LTG, VGB, GBP	LTG, VGB, CLB
Patients	Refractory epilepsy	Refractory epilepsy	Refractory epilepsy	Refractory epilepsy	Refractory epilepsy
Treatment pathways	Continuous treatment	Continuous treatment	Continuous treatment	Continuous treatment	Continuous treatment
Cost measures	Drugs, routine tmt, adverse effects tmt	Drugs, routine tmt	Drugs, routine tmt, adverse effects tmt	Drugs, routine tmt, adverse effects tmt	Drugs, extra visits from switching
Time period	6 months	Lifetime	10 years	1 year	1 year
Estimation method	Prospective, observational study	Decision-analytic model	Decision-analytic model	Decision-analytic model	Decision-analytic model
Outcome measures	Seizure control (≤ 50% seizure reduction)	QALY	Seizure-free days	None	Seizure control (≥ 50% seizure reduction)
Results	LTG: $2,819 TPM: $2,312	LTG: $41,343	LTG: $6.90	GBP: $1,643 LTG: $1,671 VGB: $1,715	CLB: $1,551 LTG: $2,219 VGB: $2,171

AEDs: antiepileptic drugs; LTG: lamotrigine; TPM: topiramate; VGB: vigabatrin; GBP: gabapentin; CLB: clobazam; QALY: quality-adjusted life year; tmt: treatment.

acknowledged the need to ration health care, and they believed that cost–effectiveness research is one method to achieve efficient distribution of resources.

Decision-analytic models are the most commonly used approach for economic assessment in epilepsy research to date. This technique attempts to synthesise the best data available from both randomised clinical trials and observational studies. These models compare alternative treatments by combining available data into a "simulated experiment". Each possible outcome or complication of treatment is assigned both a probability and a utility (clinical, functional or economic), based on the best available data. The validity of this process is based on the assumption that the consequences of treatment decisions can be composed into a finite set of discrete events and well-defined probabilities (39). Cost-effectiveness analyses of new antiepileptic drugs in patients with refractory epilepsy are presented in table 1. However, the studies are not comparable, as different approaches were used and the results were not expressed uniformly.

OUTLINE OF THE THESIS

This thesis contains five chapters. In this introductory chapter (chapter 1) the scope, objective and outline are described. Next, the individual research projects of the thesis are addressed in three chapters: the positioning of new antiepileptic drugs in general and lamotrigine in particular (chapter 2); the outcomes in patients using lamotrigine (chapter 3); and clinical and health policy decision making (chapter 4). The methodological framework and future perspectives are discussed in chapter 5.

Positioning of new antiepileptic drugs (Chapter 2)

Chapter 2.1 reviews clinically relevant selection criteria for new antiepileptic drugs. In chapters 2.2 and 2.3 data is used of the Dutch Information Project database, which contains dispensing information from over 5 million compulsorily insured patients. Chapter 2.2 describes the utilisation of antiepileptic drugs on a macro level, with an emphasis on the cost implications of newly–introduced drugs. Chapter 2.3 compares the prescription patterns of lamotrigine with those of three conventional antiepileptic drugs. This study specifically addresses the diffusion of lamotrigine in clinical practice, with a focus on selective prescribing and changes therein over time. Chapter 2.4 describes the patterns of lamotrigine use during the first years after introduction in the Netherlands, using prescription data of almost 3,600 lamotrigine–using patients identified from over 1,000 community pharmacies.

Outcomes in patients using lamotrigine (Chapter 3)

Chapter 3 is about the evaluation of the effectiveness of lamotrigine in daily practice. This assessment uses a phased approach, and key elements of this approach are: the recruitment of a sample of patients from the lamotrigine database and the evaluation of the differences between patients who gave informed consent and those who did not (chapter 3.1); the evaluation of the effectiveness of lamotrigine by means of a retrospective chart study (chapter 3.2); and the linking of data on clinical outcome with resources used in a cost–effectiveness study of lamotrigine (chapter 3.3). Finally, chapter 3.4 describes the validation of several prescription patterns; by comparing information from the pharmacy records with information obtained from medical charts.

Clinical and health policy decision making (Chapter 4)

Chapter 4.1 describes a survey into the awareness and acceptance among Dutch neurologists of the Lamotrigine Prescription Guideline that followed the reimbursement decision. Based on the results of this survey, interviews with several stakeholders were held by us to gain a better understanding of their perception of policy measures like prescription guidelines (chapter 4.2). Chapter 4.3 presents a decision analytic model on the use of lamotrigine as a first–line antiepileptic drug. In this chapter costs and effects of lamotrigine treatment are compared with those of the conventional antiepileptic drugs carbamazepine and valproate.

General discussion and future perspectives (Chapter 5)

Finally, in chapter 5 the theoretical framework and the generic issues from the research projects are discussed and a future perspective on the value assessment of new drugs in daily practice is presented.

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Selection criteria for new antiepileptic drugs in clinical use

2.1

ABSTRACT

Objective

In recent years, several new antiepileptic drugs have been licensed: felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin and zonisamide. This article gives an overview of the available pharmacological information on these new antiepileptic drugs. This article aims to give detailed background information on the new antiepileptic drugs, in order to enable physicians to make a rational choice out of the available drugs for individual patients. Data is provided for the different new antiepileptic drugs on mechanisms of action, efficacy in refractory partial epilepsy, efficacy in newly-diagnosed epilepsy in adults, efficacy in generalised seizure types, adverse effects, pharmacokinetics and special patient categories.

Methods

This article reviews the available pharmacological information on these new antiepileptic drugs.

Results

The new drugs have a proven efficacy as add-on drugs in patients with difficult-to-treat partial epilepsy, as 20-50% of patients treated in so-called add-on trials experience a seizure reduction of 50% or more. Relatively few trials have been conducted to evaluate them as monotherapy drugs for patients with newly diagnosed epilepsy. In the monotherapy trials that have been done, new drugs are often as efficacious as conventional drugs, but their tolerability is often better. However, methodological comments can be made about these trials.

Discussion

The conventional drugs have thus far maintained their status as first-line monotherapy drugs. However, when first-line monotherapy fails, an alternative has to be chosen out of the available conventional and new drugs.

INTRODUCTION

In the last decade, several new antiepileptic drugs have been introduced. This was a very welcome development, as no significant new antiepileptic drugs had been marketed for over ten to twenty years (this varied among countries). The conventional drugs are efficacious, but about 30% of patients with epilepsy are not adequately controlled with these drugs. Furthermore, conventional antiepileptic drugs can have serious adverse effects, such as cognitive impairment and severe idiosyncratic reactions (e.g. rash and hepatotoxicity).

The compounds that were licensed are felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin and zonisamide. In order to be licensed, these drugs had to demonstrate their efficacy in clinical trials involving adult patients with difficult–to–treat partial epilepsy. In these so–called add–on trials, the new compound is added to the existing antiepileptic medication of patients. When these studies are compared with each other, the parameter chosen for comparison is most often the proportion of patients with a decrease in seizure frequency greater than 50%. These new antiepileptic drugs accomplish such a reduction in 20–50% of the patients; representative trials are cited in the reference list (1–9). Different authors of relevant review papers have used different add–on studies to compare the new antiepileptic drugs (10,11). The selection of trials cited here is based on our opinion of the appropriateness of the titration schedules and the maintenance dosages that were used. New antiepileptic drugs are always tested in add–on trials first, because it is considered unethical to administer these drugs in monotherapy when their efficacy has not yet been established. The disadvantage of add–on trials is that they give only a rough idea of the efficacy and the adverse effects of a specific compound, as the effects seen in these trials are effects of combinations of drugs. Furthermore, unexpected or idiosyncratic adverse effects may become apparent only after licensing, as registration files typically contain data of at most 2,000 patient years, and many idiosyncratic reactions have a lower incidence. This was the case for felbamate and vigabatrin (12). Felbamate is associated with a relatively high incidence of aplastic anaemia (± 0.5 to 1 per 10,000 patients treated) and hepatic failure (± 1 per 10,000 patients treated) and vigabatrin is associated with a high incidence of irreversible visual field defects after chronic use (20–40%) (13,14). The use of these compounds has been restricted to severe refractory partial epilepsy and to the syndromes of Lennox–Gastaut (felbamate) and West (vigabatrin).

Most of the new antiepileptic drugs have not been evaluated extensively as monotherapy drugs in adult patients with newly diagnosed partial epilepsy. There are even less studies which have evaluated new antiepileptic drugs in patients who failed to respond to their first antiepileptic drug. Currently, such conventional antiepileptic drugs as carbamazepine, phenytoin and valproate maintain their first–line status.

Table 1. Mechanisms of action of antiepileptic drugs

Antiepileptic drug	State-dependent blockade of sodium channel	T-type calcium channel blockers	Non-T-type calcium channel blockers	Enhancing GABAergic inhibition	Reduction of glutamate-mediated excitation
Sodium channel blockers					
Carbamazepine (CBZ)	+++			+	+
Phenytoin (PHT)	+++		+	+	
Lamotrigine (LTG)	+++			+	+
Oxcarbazepine (OXC)	+++		+		+
Multiple mechanisms of action					
Phenobarbital (PB)/ Primidon (PRM) *	++		+	++	++
Gabapentin (GBP)	+		+	++	+
Topiramate (TPM)	++		+	++	++
Valproate (VPA)	++	+		++	+
GABAergic drugs					
Clonazepam (CLZP)/ Diazepam (DZP)	+		+	+++	
Tiagabine (TGB)				+++	
Vigabatrin (VGB)				+++	
Other					
Ethosuximide (ESM)		+++			
Felbamate (FBM)	+		+	+	++
Levetiracetam (LEV)			+	++	
Zonisamide (ZSM)	++	++			

* Phenobarbital is the major active metabolite of primidon.
It is uncertain to which extent primidon itself contributes to efficacy and to toxicity.

+++ Well-documented action believed to account for a major part of the drug's anticonvulsant effect;

++ Effect probably of clinical significance;

+ Effect only tentatively characterized or seen only in supratherapeutic concentrations.

When carbamazepine, phenytoin or valproate fail because of a lack of seizure control and/or because of adverse effects, another drug must be chosen out of the other conventional drugs or out of the new ones. This article gives an overview of the available pharmacological information on these new antiepileptic drugs. This information should assist physicians in the choice between the available antiepileptic drugs for each individual adult patient. We have focused on mechanisms of action, efficacy, specific adverse effects, pharmacokinetic properties and patient characteristics.

MECHANISMS OF ACTION

Knowledge of the pathophysiology of epilepsy and the mechanisms of action of antiepileptic drugs is still incomplete. The main mechanisms of action of the available antiepileptic drugs are thought to be: blocking voltage–dependent ion channels (sodium, potassium and calcium channels), increasing the activity of the inhibitory GABA (gamma–aminobutyric acid)–ergic system and decreasing the activity of the excitatory glutamatergic system (15,16). The mechanisms of action of the new antiepileptic drugs show some overlap with the longer existing compounds, as is shown in table 1 (16–19). The potentially most important mechanisms of action of certain antiepileptic drugs are not shown in the table. Gabapentin, for example, binds to a protein subunit of voltage–gated calcium channels and the mechanism of action of levetiracetam is largely unknown (20). Selective blockade of N–type calcium channels by levetiracetam has recently been described (21). A review of clinical studies suggested that a combination of a sodium channel blocker with a drug that increases the GABA–ergic neurotransmission or that has multiple mechanisms is generally more effective than a combination of two sodium channel blockers (22). However, as the relative contribution of different mechanisms of action to the anticonvulsant effect is controversial for many of these drugs, it is currently more appropriate to judge each individual combination on its own merits. In agreement with the aforementioned review (22), Stephen and Brodie have found that the most effectual combinations in their epilepsy unit were valproate+lamotrigine, valproate+carbamazepine, carbamazepine+gabapentin and phenytoin+phenobarbital (23). Wong has found that among lamotrigine users, patients who were not taking concurrent carbamazepine were three times more likely to become seizure–free than those who were (24).

EFFICACY

The efficacy of antiepileptic drugs is usually assessed in two subpopulations of epilepsy patients: patients with difficult–to–treat partial epilepsy and patients with newly–diagnosed epilepsy.

Refractory partial epilepsy

Marson et al. have evaluated the efficacy of several new antiepileptic drugs (gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin, zonisamide) in a meta–analysis of add–on trials (10). In this analysis, these antiepileptic drugs showed efficacy in 20–40% of patients with refractory partial epilepsy (i.e. more than 50% seizure reduction). The efficacy and/or adverse drug reactions did not differ statistically between the compounds. A trend was noted in which topiramate and vigabatrin show higher

efficacy than the other compounds, but they also tended to be associated with more adverse effects. Marson et al. have also reviewed add–on studies involving levetiracetam, oxcarbazepine, remacemide and zonisamide (25).

In recent years it has become clear that several compounds were not administered optimally in the add–on studies that were reviewed. Gabapentin, for example, can be given in higher dosages than were used during the trials reviewed, while lamotrigine and topiramate are presently given at slower dose titration schedules to avoid or limit the adverse drug reactions. Also, patients who used valproate were excluded from a large lamotrigine add–on trial, while lamotrigine/valproate is an effective combination (3). Therefore the results of this meta–analysis are of limited use. The calculation of the 'number needed to be treated' for each compound based on this meta–analysis therefore also has only limited validity (26). Cramer et al. reviewed only "key" add–on trials of new antiepileptic drugs, but found that comparison was difficult due to differences in methodology, in baseline characteristics of patients and in reporting of data between trials (11).

Recently, a number of papers have been published which report the retention time of several new antiepileptic drugs in patients with difficult–to–treat partial epilepsy (27–32). Retention time is the period of time that a patient continues to use a drug. It is considered to be a global means of measuring effectiveness, as it expresses both efficacy and tolerability (33). Lamotrigine was less likely to be discontinued than gabapentin and vigabatrin in some of these studies. These studies may suffer from survival bias: the new antiepileptic drugs were not licensed simultaneously, which means that persons who reacted favorably to a previously licensed antiepileptic drug were no longer available for trials with drugs introduced afterwards. These drugs may also have been administered with titration rates and maintenance doses which are no longer recommended. It should be mentioned that topiramate performed better than lamotrigine and gabapentin in one study and that the recently licensed levetiracetam achieved better seizure–free rates in a "continuation study" than previously licensed antiepileptic drugs had done (32).

Czapinski has evaluated the effectiveness of the first new antiepileptic drug given to patients with drug–resistant partial epilepsy (34). The percentages of seizure–free patients were 31% for tiagabine; 28% for gabapentin; 27% for topiramate; 21% for lamotrigine and 16% for vigabatrin. Topiramate led to the most withdrawals (18%, compared with 2–7% for the other drugs). It must be noted that drug–resistance was defined as a failure for one or two conventional drugs; this appears to be a less refractory population than patients usually included in add–on trials.

Newly-diagnosed epilepsy

A number of monotherapy studies have been performed in which a new drug has been compared with one of the conventional compounds (table 2) (35–44). The main means of expressing the outcome in most of the studies was by the percentage of

Table 2. Comparative monotherapy studies

Antiepileptic drugs	Ref. nr.	Patients	Starting doses	Titration	Evaluation period	Seizure free	Failures caused by ADR
GBP 300, 900 or 1800 mg/day vs CBZ 600 mg/day	35	292 de novo patients with partial epilepsy; age ≥ 12 years	Not reported	GBP in 1 week to end dose; CBZ in 3 weeks to end dose	24 weeks	Not reported	300 mg: 0%; 900 mg: 4%; 1800 mg: 14%; CBZ: 24%
GBP vs LTG (flexible dosages)	36	291 de novo patients with partial seizures and generalised tonic seizures	Not reported	GBP in 2 weeks to 1800 mg/day and LTG in 6 weeks to 150 mg/day; followed by 12 week dose adjustment phase	12 weeks	GBP: 54% LTG: 51%	GBP: 9% LTG: 10%
LTG vs CBZ (flexible dosages)	37	260 de novo patients with partial seizures and generalised tonic seizures; age ≥ 12 years	LTG: 50 mg CBZ: 200 mg	LTG: 50 mg / week and CBZ: 200 mg / week; followed by a 20 week dose adjustment phase	24 weeks	LTG: 39% CBZ: 38%	LTG: 15% CBZ: 27%
LTG 100 or 200 mg/day vs CBZ 600 mg/day	38	343 untreated patients with partial seizures and generalised tonic seizures; age ≥ 12 years	LTG: 25 mg CBZ: 200 mg	LTG: 25 mg / 2 weeks; CBZ: 200 mg / 2 weeks	24 weeks	LTG 100 mg: 51% LTG 200 mg: 60% CBZ 600 mg: 55%	LTG 100 mg: 4% LTG 200 mg: 5% CBZ 600 mg: 10%
LTG vs CBZ (flexible dosages)	39	150 patients with newly diagnosed epilepsy; age ≥ 65 years	LTG: 25 mg CBZ: 100 mg	LTG: 25 mg / 2 weeks; CBZ: 100 mg / 2 weeks		LTG: 39% CBZ: 21%	LTG: 18% CBZ: 42%
LTG vs PHT (flexible dosages)	40	181 de novo patients with partial seizures and generalised tonic seizures; age 14-75 years	LTG: 100 mg PHT: 200 mg	LTG was increased to 150 mg / day and PHT to 300 mg/day after 2 weeks; followed by 22 week dose adjustment phase	24 weeks	LTG: 43% PHT: 36%	No difference
OXC vs CBZ (flexible dosages)	41	194 de novo patients with partial seizures and generalised tonic seizures; age 15-65 years	CBZ: 200 mg OXC: 300 mg	Weekly intervals during 4-8 weeks	12-48 weeks	OXC: 46% CBZ: 49%	OXC: 14% CBZ: 25%
OXC vs PHT (flexible dosages)	42	237 de novo patients 16-65 years	OXC: 300 mg PHT: 100 mg	Flexible; maintenance dose 900-2400 mg OXC or 150-800 mg PHT		OXC: 59% PHT: 58%	OXC: 4% PHT: 11%
OXC vs VPA (flexible dosages)	43	212 de novo patients with partial seizures and generalised tonic seizures; age 15-65 years	OXC: 300 mg VPA: 300 mg	Biweekly intervals during 8 weeks	48 weeks	OXC: 57% VPA: 54%	OXC: 12% VPA: 8%
TPM 100 or 200 mg/day vs CBZ 600 or VPA 1250 mg/day	44	623 patients with newly diagnosed epilepsy epilepsy	Not reported	Not reported	6 months	TPM 100 mg: 44% TPM 200 mg: 49% CBZ: 44% VPA: 44%	TPM 100 mg: 19% TPM 200 mg: 28% CBZ: 25% VPA: 23%

seizure-free patients during a pre-determined evaluation period. As can be seen in the table, some trials only included patients with newly-diagnosed partial epilepsy, whereas in other trials patients with newly-diagnosed primary generalised tonic-clonic seizures were also included.

Comparative monotherapy studies enable a more straightforward comparison of the effectiveness of drugs. Alas, differences in titration schedules, in maintenance dosages and in study scheme make it difficult to compare the results of these studies. Table 2 shows that none of the newer antiepileptic drugs has superior efficacy compared with the older compounds. The trials listed in table 2 do suggest that fewer patients using gabapentin, lamotrigine or oxcarbazepine withdraw from treatment than patients using carbamazepine or phenytoin. The tolerability of valproate appears to be comparable to that of the new compounds. However, it is doubtful whether carbamazepine in particular was given the same "chance" of success in these studies. The dose increases for carbamazepine occurred fairly rapidly in most of these trials, while the titration schedules of the newer drugs have been adjusted to reduce treatment failure due to adverse effects (45). Furthermore, carbamazepine was not applied in currently available slow-release or long-acting forms. This may have increased its number of adverse effect-related treatment failures.

Kwan and Brodie have recently reported about their experiences with first-line drugs in their epilepsy unit (46): 61.5% of the 78 de novo patients treated with lamotrigine became seizure free (10% of the withdrawals due to adverse effects), whereas only 41.5% of the 212 patients treated with carbamazepine became seizure free (with 27% withdrawing because of adverse effects). Valproate performed similarly to lamotrigine, with 57% of the 101 patients becoming seizure free and 13% withdrawing because of adverse effects. 26%, 25% and 26% respectively withdrew because of inadequate seizure control. However, an unknown proportion of these patients participated in two of the aforementioned trials. It is possible that a more conservative titration schedule and use of controlled-release formulations would have lowered the withdrawal rate of carbamazepine.

In the only head-to-head comparison between two new antiepileptic drugs published to date, lamotrigine and gabapentin showed similar effectiveness in previously untreated patients (36).

Generalised epilepsy

Felbamate may be effective in a range of generalised seizure types, but due to the risk of serious adverse effects, felbamate is only used for patients with malignant epilepsies, such as West and Lennox-Gastaut syndrome, who have continued seizures on other drugs. Gabapentin has no effect on absence or myoclonic seizures (47,48). It did reduce primary generalised seizures more than placebo; however this difference was not statistically significant (47).

Lamotrigine is efficacious for all generalised seizure types (49–51). The best responses have been noted in typical and atypical absence seizures and in atonic seizures. It is not administered as a first–line drug, but may be given as an add–on when valproate or another first–line drug fails. When the combination with lamotrigine is successful, an attempt may be made to withdraw the first–line drug. Although lamotrigine has been reported to be efficacious in juvenile myoclonic epilepsy (52), it seems less efficacious than valproate (53). Biraben and colleagues treated 7 juvenile myoclonic epilepsy patients with lamotrigine, and all 7 patients worsened (54). As lamotrigine can worsen myoclonic seizures, it should not be used in severe myoclonic epilepsy. Patients with photosensitivity may benefit from lamotrigine, especially when it is used in combination with valproate.

Levetiracetam has shown promise in several generalised seizure types, but data is limited (55–57). Oxcarbazepine may be given to patients who have idiopathic generalised tonic–clonic seizures, but it may worsen absence and myoclonic seizures (58). Tiagabine has no indication for patients with primary generalised epilepsy. It has been reported to induce absence status epilepticus in these patients.

Topiramate is efficacious against generalised tonic–clonic seizures, myoclonic seizures and in Lennox–Gastaut and West syndromes (59–61). It is a drug that may be helpful after first–line drugs have failed (58). Dooley et al. have warned that, although topiramate may be efficacious in intractable childhood epilepsy, the associated adverse effects were considerable (62). A recent study has shown that topiramate may also be efficacious for absence seizures (63).

Some experts consider vigabatrin, which is administered primarily for tuberous sclerosis, also to be a first–line drug for West syndrome (64,65). It may also be used in patients with idiopathic infantile spasms refractory to ACTH or valproate (65). However, the steering committee of the United Kingdom Infantile Spasm study claims that there is no evidence that vigabatrin is a better treatment for infantile spasms than ACTH (66). The steering committee challenges the claim that vigabatrin is the drug of choice for infantile spasms because vigabatrin has also been reported to lead to concentric visual field defects in children. As visual field testing is not feasible in small children, one has to rely on less appropriate tests in these patients (visually evoked potentials and electroretinography) (67). Irrespective of the use of vigabatrin in West syndrome, vigabatrin has been reported to worsen absence and myoclonic seizures (58). Zonisamide seems to be efficacious in most generalised seizure types; the evidence is however limited (68,69). It may be used as a third line drug for generalised epilepsy. It appears to be particularly potent in progressive myoclonic epilepsy (69).

ADVERSE EFFECTS

Neurotoxicity

Dose–related neurotoxic adverse effects, such as cognitive impairments, diplopia, headache, fatigue and sedation, characterize the use of the older generation of antiepileptic drugs. Neurotoxicity is also the most frequently occurring type of adverse effect for the new compounds, although the frequency of these adverse effects differs between the compounds. In addition to these general neurotoxic adverse effects, each of the new compounds has its own specific adverse effects, which can be either neurotoxic or systemic.

Felbamate was associated with dizziness in more than 5% of the patients that received the drug as adjunctive therapy (70). Gabapentin is tolerated well by most patients, as was shown by the monotherapy trials (35,36). It may lead to adverse effects, such as somnolence, dizziness and ataxia quickly after the start of treatment (71), and therefore we recommend a more conservative titration schedule than the manufacturer does. Ramsay and Pryor have reported the occurrence of oscillopsia and diplopia when gabapentin is administered to patients with high plasma levels of carbamazepine (71). An increase in fatigue may also occur when using this combination.

Lamotrigine is well tolerated by most patients (36–40,46,72). It can lead to dosage–related neurotoxic adverse effects (e.g. dizziness and ataxia) when used in combination with carbamazepine of phenytoin. Lowering the dosage of the conventional drug may reverse these adverse effects (73). Comparative studies (table 2) show less cognitive side effects for gabapentin and lamotrigine compared with conventional antiepileptic drugs.

Levetiracetam has not yet been evaluated as monotherapy for newly diagnosed patients, but appears to have little detrimental effect on cognitive abilities. Somnolence, headache and dizziness can be encountered in patients who start with levetiracetam (74). A pharmacodynamic interaction may cause or increase adverse effects when levetiracetam is added to carbamazepine (75).

Oxcarbazepine is structurally related to carbamazepine, and these drugs have a same range of neurotoxic adverse effects (41). Due to the methodological limitations of the monotherapy trials comparing new to old compounds, superior effectiveness has not (yet) been demonstrated for oxcarbazepine compared to carbamazepine (41). Dizziness and asthenia are the most frequently encountered neurotoxic adverse effects associated with the use of tiagabine, but this drug has a favorable cognitive profile (76).

Topiramate is known for neurotoxic adverse effects such as paresthesias and psychomotor slowing, and these can be serious handicaps for patients. The current slower titration rate and lower daily dosages may reduce these adverse effects (77). In a study with a limited number of adult volunteers the cognitive effects of gabapentin, lamotrigine and topiramate have been compared directly (78). Gabapentin and

lamotrigine seem to have a more favorable profile when compared with topiramate.

It is likely that the use of vigabatrin may lead to psychosis (67). Zonisamide may have detrimental effects on verbal learning, but a slower titration rate may help decrease this. The use of zonisamide may lead to irritability, depression, anxiety or psychosis. This may be related to its effects on the synthesis and degradation of monoamine neurotransmitters (79).

Besag has reviewed the behavioral effects of new antiepileptic drugs (80). Epilepsy patients seem to be at greater risk of behavioral adverse effects than patients with other CNS conditions. Gabapentin, oxcarbazepine and especially lamotrigine can induce mood improvement, although insomnia and aggressive behavior have been reported as well (80). Topiramate is associated with a higher frequency of psychosis. Tiagabine may induce depressions in some patients, but, as for levetiracetam, experience is limited (80).

Ketter et al. have proposed to select antiepileptic drugs based on their 'sedatory' or 'stimulating' effects (81): a patient who is rather inactive should be prescribed a 'stimulating' antiepileptic drug and vice versa.

Systemic side effects

Currently 36 cases of aplastic anemia and 18 cases of hepatic failure have been reported in patients receiving felbamate (82). Rash is a well–known idiosyncratic adverse effect of the old generation of antiepileptic drugs. Rash can occur with lamotrigine and oxcarbazepine; it seldom occurs with zonisamide and very seldom with gabapentin. A low starting dose and slow titration are factors that reduce the incidence of rash. Severe lamotrigine–induced rashes (even fatal Stevens–Johnson and Lyell syndromes) still occur despite of these measures. Rash does not seem to occur with levetiracetam, tiagabine, topiramate or vigabatrin.

The risk of gabapentin and vigabatrin is that they may cause body weight gain (83). Mild infections have been reported for levetiracetam, mostly upper respiratory tract infections, such as rhinitis and flu– like symptoms (74). The underlying cause is unclear and these symptoms are not related to changes in white blood cell or neutrophil counts (84). This is generally not an adverse effect that necessitates treatment withdrawal (77). Oxcarbazepine is associated with hyponatremia, an adverse effect that usually does not lead to clinical symptoms. In the elderly however, it may lead to an encephalopathic syndrome.

Diarrhea has been reported as a result of the use of tiagabine (76). Recently, a case report was published of asymptomatic visual field defects associated with tiagabine; the defects reversed upon discontinuation of tiagabine (85). However, tiagabine was not associated with visual field effects in larger patient series (86). Sills et al. have reported that tiagabine does not increase GABA levels in the retina and does not accumulate in the retina; vigabatrin does both these things (87).

Well–known systemic adverse effects of topiramate are weight loss and the risk of the development of renal stones. In a pooled analysis of add–on trials, weight loss ranged from 1.6 to 5.6 kilograms (88). Weight loss appears to be greatest in patients who are heavier at onset and patients who use higher dosages, while it is most commonly seen in female patients (88, 89). Weight loss may be very severe. There have been several case reports of angle–closure glaucoma associated with topiramate use; one example is included in the reference list (90).

Vigabatrin is associated with the development of concentric visual field defects after chronic use in up to 20 – 40% of the patients. The use of zonisamide is associated with weight loss (in 3 – 21% of the patients) and sporadically with hematogical disorders (such as leukopenia) and renal calculi (79). The risk of renal calculi seems to be higher in patients from Europe and the United States than in patients from Japan, where the drug has been licensed since 1989 (79).

Dose titration and side effects

The experiences from the large add–on trials have led to changes in the titration schedules for lamotrigine, tiagabine and topiramate, because of the occurrence of rash (lamotrigine) and dose–related side effects in general (tiagabine, topiramate). It therefore now takes six weeks or more before these drugs can be administered in therapeutic doses (91). This may limit the use of these drugs in patients with low seizure frequencies. The manufacturers of gabapentin and levetiracetam recommend titration schedules of only a few days before reaching the first maintenance dose (900 mg/day and 1000 mg/day respectively); clinical experience leads us to believe that a more conservative approach is to be preferred (this is the authors' personal experience).

PHARMACOKINETICS

The complex pharmacokinetics of the old generation antiepileptic drugs hamper the use of these drugs. Disadvantages are a high protein binding (phenytoin, valproate), non–linear kinetic profile (phenytoin) and a high potential for interactions (phenobarbital, phenytoin, carbamazepine) (92). This high interaction potential is due to the fact that these drugs induce and are metabolised by the cytochrome P450 system. The new antiepileptic drugs generally have a more favorable pharmacokinetic profile, which is shown in table 3 (82,92). Bioavailability is generally high, with the only exception for gabapentin in higher dosages, caused by saturation of the absorption. Nutrition hardly interferes with the absorption of these compounds (92). Protein binding is low, with the exception of tiagabine, so there is generally no risk for changes in the free fraction through interaction with co–medication. Most of the drugs have relatively short elimination half–life times; only gabapentin and tiagabine need more then two daily dosing caused by short half–life times (92).

Table 3. Pharmacokinetic characteristics

	Bioavailability	Protein binding	Half-life ($t_{1/2}$)	Metabolism	Route of elimination	TDM[1] range
Felbamate	Over 90%	22-36%	14-23 hours	Inactive metabolites via different metabolic pathways	40-50% unchanged in urine	?
Gabapentin	35-60% (dose dependent saturable absorption)	None	5-7 hours	None	Unchanged in urine	Cmin > 2 µg/ml
Lamotrigine	98%	55%	24-31 hours in monotherapy; 15 hours with enzyme-inducers[2]; 59 hours with valproate	85% glucuronidation into inactive metabolites	94% in urine; 76% as 2-N-glcuronide, only 10% unchanged	2 – 15 µg/ml
Levetiracetam	>95%	None	6-8 hours	Partly hydrolysed in blood into inactive metabolite	66% unchanged in urine; 27% as metabolite in urine	Unknown; Possible Cmin > 10 µg/ml
Oxcarbazepine	>95%	40% (MHD[3])	MHD: 8-12 hours	Rapid, nearly complete transition into active MHD; no epoxides	1% unchanged in urine; 45% as MHD in urine	MHD: 10 – 35 µg/ml
Tiagabine	90%	96%	4-13 hours in monotherapy; 2-5 hours with enzyme-inducers[2]	Nearly totally metabolised into inactive metabolites	25% in urine (<1% unchanged), 63% in faeces	No TDM range; indirect effect
Topiramate	81-95%	9%-17%; significantly and saturably bound to erythrocytes	20-30 hours; 8-15 hours with enzyme-inducers[2]	Partly converted into inactive metabolites	60-80% unchanged in urine	?
Vigabatrin	At least 60-80%	None	5-8 hours	None	60-80% unchanged in urine	No TDM range; indirect effect
Zonisamide	Complete	40-60%; highly concentrated in erythrocytes	50-60 hours; 27-38 hours with enzyme inducers[2]	Various metabolic pathways	>80% in urine (30% unchanged)	15-30 mg/l

[1] TDM: therapeutic drug monitoring

[2] Enzyminducers; this concerns the antiepileptic drugs carbamazepine (CBZ), phenobarbital (PB), phenytoine (PHT) and primidon (PRM)

[3] MHD: monohydroxy derivative; the active metabolite of oxcarbazepine

The new compounds have fewer interactions with concurrent medication then conventional antiepileptic drugs do, with the possible exception of felbamate. Tiagabine and lamotrigine do show interactions with other antiepileptic drugs. Enzyme–inducing antiepileptic drugs such as carbamazepine and phenytoin reduce the half–life times of these drugs considerably. The concentration of tiagabine or lamotrigine is reduced by approximately 50% when compared with monotherapy. In cases where lamotrigine is used together with valproate, lamotrigine levels are about twice as high as in lamotrigine monotherapy. There is uncertainty whether the high effectiveness of the valproate /lamotrigine combination is due to this pharmacokinetic interaction alone; there might very well also be a pharmacodynamic interaction (93).

Oxcarbazepine and topiramate show some enzyme–inducing activity, and in cases when these drugs are combined with oral contraceptives or oral anticoagulants, doses need to be adjusted. Oxcarbazepine, because of its lesser enzyme induction, is an appropriate alternative for carbamazepine when co–medication makes this relevant.

The available therapeutic ranges for the new antiepileptic drugs should be interpreted with care, as these values are based on patients with severe epilepsy treated with several antiepileptic drugs (94). There is considerable overlap between responders and non–responders and between patients with and without adverse effects for felbamate, lamotrigine, oxcarbazepine and zonisamide. The serum levels vary greatly between patients responding to gabapentin. For levetiracetam and tiagabine there is little information. As vigabatrin's mechanism of action is irreversible GABA–transaminase inhibition, its serum levels give no indication for its effect.

SPECIAL PATIENT POPULATIONS

The risk of certain adverse effects may be higher in certain sub–populations. One will want to avoid tiagabine in patients with a history of psychosis, and topiramate in patients with a history of renal stones.

Several conventional drugs have the advantage of different formulations. An intravenous formulation is important during surgery. The availability of a drug in a solution can be necessary for children and patients with a mental or physical handicap.

Elderly: The adverse effects of the new drugs on the elderly still awaits extensive evaluation. The elderly appear to have relatively good tolerability for gabapentin and lamotrigine, which, together with valproate and carbamazepine, are deemed first–line anticonvulsants in these patients (95). Oxcarbazepine has the risk of hyponatremia and topiramate may cause cognitive problems in the elderly (95). Data on levetiracetam, tiagabine and zonisamide is incomplete in this respect.

Decreasing organ functions will influence the clearance of drugs and must be taken into account. A number of drugs have a relative contra–indication for patients with a

decreased renal function. Dosage adjustments and extra attention are necessary for gabapentin, levetiracetam, oxcarbazepine, topiramate and vigabatrin in these patients. Concerning liver function, the metabolisation of a drug will usually be influenced only when that function is in an advanced state of impairment. In those cases, it is better to use a drug that is not or hardly metabolised by the liver (such as gabapentin, levetiracetam or topiramate).

Women in childbearing age: There is controversy regarding the question whether use of valproate is associated with a higher incidence of polycystic ovary syndrome (PCOS) (96, 97). Herzog and Schacter conclude that, despite limitations in studies reporting an association between use of valproate and occurrence of PCOS, the evidence cannot be entirely dismissed (98). As valproate also has teratogenic effects, it may be concluded that it is less suitable for women of childbearing age. Lamotrigine has been positioned as a better alternative for this group. It does have certain advantages, such as its relative lack of adverse effects and its lack of enzyme induction. It may cause a worsening of acne. Based on limited pregnancy data, lamotrigine does not seem to have a major teratogenic effect (99). There is no good reason for avoiding lamotrigine in women who wish to get pregnant, given the known effects of the conventional antiepileptic drugs.

The problem with lamotrigine and [even more with] the other new antiepileptic drugs is that only limited data is available regarding their teratogenic effects. Retrospective data is available, but should be treated with caution and take its selection bias into account. Women with epilepsy who become pregnant should be encouraged to enroll in prospective pregnancy registries (such as the Antiepileptic Drug Pregnancy Registry in North America and EURAP in Europe).

Two different attitudes can be taken towards the problem of possible teratogenic effects of new antiepileptic drugs. One is that the new antiepileptic drugs should be avoided in women who wish to become pregnant, since the risks for birth defects are not known. The other is that the conventional antiepileptic drugs should be avoided in these patients, because their risks are known to be relatively high. Whatever the compound used, recommendations are still valid for the use of drugs in monotherapy, in low doses, and divided over the day. It is known that topiramate and zonisamide are teratogenic in animals, whereas other drugs are less or not teratogenic in animals (82). Oxcarbazepine and topiramate are enzyme–inducers, which is important in women using oral anticonception.

Children: For efficacy in partial seizure and generalised seizure types see the relevant paragraph. Young children in particular have a higher clearance than adults and therefore they may need higher dosages per kilogram.

Lamotrigine has few cognitive effects and it is efficacious in children with partial epilepsy and in children with generalised epilepsy. The slow titration rate and the risk of severe rashes (which seems to be higher in children) are disadvantages. There is sufficient evidence for the effectiveness of oxcarbazepine in children with partial

Table 4. Selection criteria for new AEDs

Name	Indication partial epilepsy	Indication generalised epilepsy	Contra-indications	Main mechanism of action[1]	Minimal titration period add-on therapy	Most important adverse drug reactions[2]	Considerations
Felbamate	Intractable partial epilepsy in adults	Lennox-Gastaut when primary AEDs have failed (age > 4 years)	Absolute: history of hemato-logical disease, liver disease or autoimune disease; Relative: history of renal disease	Multiple	1 day	Aplastic anemia, hepatotoxicity, nausea, weight loss, insomnia	Hematologic and liver function tests should be carried out prior at and frequently after the start of FBM; patients and family should be educated about warning symptoms that might herald either hematologic or hepatic toxicity
Gabapentin	Add-on	None	Relative: Renal disease	Multiple	1 week	Nausea, malaise	3x daily dosing schedule. When titrated over a period of 1 week to 3 x 300 mg/day well tolerated. May combine well with CBZ.
Lamotrigine	Mono-therapy or add-on	All seizure types when first line drug has failed	Absolute: severe myoclonic epilepsy; Relative: patients with rash on PHT or CBZ; liver disease	Sodium channel	> 6 weeks	Rash, irritability, insomnia	Long titration period. Well tolerated. May combine well with VPA. Less suited for patients on CBZ?
Levetiracetam	Add-on	None so far	Relative: renal disease	Unknown	1 week	Infection such as rhinitis or flue-like symptoms	Titration: 1st 7 days 2 x 250 mg/day; after a week to 2 x 500 mg/day
Oxcarbazepine	Mono-therapy or add-on	Tonic-clonic seizures when first line drug has failed	Absolute: absence or myoclonic seizures; Relative: renal disease; patients on a sodium-limited diet or on drugs than lead to hyponatremia (lithium, diurectics)	Sodium channel	2 weeks	Rash (less frequent than with CBZ and in 25% cross reaction); hyponatremia (more frequent compared to CBZ)	As effective as CBZ. Less adverse effects at high dosages?
Tiagabine	Add-on	None	Absolute: absence or myoclonic seizures; Relative: Liver disease, history of depression	GABA	> 6 weeks	Diarrhoea, dizziness	3-4 x daily dosing. Long titration period.
Topiramate	Add-on	All seizure types (except absence) when first line drug has failed	Relative: history of psychiatric disease, renal disease, (family) history of renal calculi.	Multiple	> 6 weeks	Paresthesias, cognitive effects, weight loss, kidney stones, metabolic acidosis in children, psychosis	Long titration period. Relatively severe neurotoxic adverse effects
Vigabatrin	Intractable partial epilepsy in adults	West syndrome (especially when secondary to tuberous sclerosis)	Absolute: absence or myoclonic seizures; Relative: history of psychiatric disease, renal disease	GABA	1 day	Concentric visual field defects (in as many as 40% of patients), psychosis	Visual field testing should be carried out prior to and at regular intervals after the start of VGB
Zonisamide	Add-on	All seizure types when first and second line drugs have failed	Relative: history of psychiatric disease; renal disease; family) history of renal calculi	Multiple	2 weeks	Weight loss, kidney stones, oligohydrosis in children, psychosis	Experience is still limited, as this drug has only been licensed in Japan for a long period

[1] There is some evidence that sodium channel blockers should be combined with a multiple-mechanism drug or with one that has an predominantly affects the GABA system (and vice versa).

[2] In addition to neurotoxic adverse effects shared by other antiepileptic drugs, such as drowsiness, dizziness and ataxia

epilepsy (100). Topiramate may provoke metabolic acidosis and central hyperventilation in small children (101). There is insufficient data for the other new compounds.

The mentally handicapped: Recent studies in this population suggest that gabapentin, lamotrigine and topiramate are effective in this population (102,103). Oxcarbazepine is also an effective drug for this type of patient (104). There is insufficient data for levetiracetam, tiagabine and zonisamide. The agitation sometimes caused by certain antiepileptic drugs merits extra caution in this population (105).

CONCLUSIONS

The choice for second–line antiepileptic drugs depends on individual patient characteristics and on the characteristics of the individual drugs. The data presented in this article, which is summarised in table 4, should assist physicians in making a rational choice. Please note that licensed indications can vary per country.

Some general conclusions may be drawn

1. Effectiveness in refractory partial epilepsy: The 9 new antiepileptic drugs have proven efficacy in patients with intractable epilepsy. FBM and vigabatrin are no longer routinely used because of their idiosyncratic adverse effects.
2. Effectiveness in newly diagnosed epilepsy: The only new compounds, which have been evaluated extensively as monotherapy drugs for partial seizures and generalised tonic-clonic seizures, are lamotrigine and oxcarbazepine. These drugs seem to have comparable efficacy to carbamazepine and phenytoin, but more favorable tolerability. Efficacy and tolerability are comparable to valproate. As there are methodological limitations to these studies, there is no conclusive data to prefer these drugs as first-line drugs, except when there are specific reasons to choose them.
3. Some new antiepileptic drugs are very useful second-line drugs for generalised seizure types, whereas other new drugs have no use or are contra-indicated. It is currently being debated whether vigabatrin is the best first-line treatment of infantile spasms.
4. Tolerability: The new drugs seem to be tolerated well, but they all have specific adverse effects which may make them less suited for individual patients. Slower titration rates seem to improve the tolerability of many of these drugs. Physicians should realise that the severe adverse drug reactions of vigabatrin became apparent only after these drugs had been available for several years.
5. Most new drugs have a straightforward pharmacokinetic profile and a low potential for interactions.

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The impact of new antiepileptic drugs on the volume and cost of pharmaceutical care in the Netherlands

2.2

ABSTRACT

Objective

In the past decade, several new antiepileptic drugs (AEDs) were introduced in the Netherlands. These new drugs, one of which is lamotrigine, are 5 to 20 times more expensive than conventional anticonvulsants. In 1997, the high cost of lamotrigine, together with a lack of clinical data supporting its superiority over conventional drugs, prompted the Dutch Health Insurance Board to release a guideline in which the use of lamotrigine was restricted to difficult-to-treat patients. Other new drugs that were marketed after 1997 also became subject to this guideline. The utilisation of new antiepileptic drugs and the consequences for the cost of pharmaceutical care are the subject of this paper.

Methods

Data from extramurally prescribed antiepileptic drugs was obtained from the Dutch Drug Information Project, which is a database containing prescriptions for about 5.5 million inhabitants of the Netherlands. This data was used to study the impact of new antiepileptic drugs on volume and costs of pharmaceutical care in the period from 1995 to 2001 in the Netherlands.

Results

Between 1995 and 2001, the total volume of antiepileptic drugs increased by 130%, 60% of which consisted of new antiepileptic drugs. Gabapentin, lamotrigine and oxcarbazepine were the most frequently prescribed new compounds. The volume share of new antiepileptic drugs increased from 5% in 1995 to 18% in 2001. The cost of pharmaceutical care amounted to € 21.5 million in 1995 and rose to € 47 million in 2001; 80% of this increase was due to the introduction of new antiepileptic drugs.

Discussion

Although in 2001 the volume share of new antiepileptic drugs was still modest, their introduction has led to a strong increase in the cost of pharmaceutical care. New data is emerging on the effectiveness and cost-benefit sum of the new antiepileptic drugs; this may change the place in therapy of these drugs. Because of their strong potential to force up cost, the positioning of new antiepileptic drugs requires further attention.

INTRODUCTION

Pharmacotherapy represents the first-line option in the management of epilepsy, a common, heterogeneous neurological disorder. For 25 years, four drugs have dominated

Table 1. Antiepileptic drugs in the Netherlands

Year of introduction	Name		ATC	DDD (mg)	Drug cost[1]
1912	Phenobarbital	(PB)	N03AA02	100	2.41
1938	Phenytoin	(PHT)	N03AB02	300	2.73
1958	Ethosuximide	(ESM)	N03AD01	1250	15.45
1964	Carbamazepine	(CBZ)	N03AF01	1000	14.73
1971	Valproate	(VPA)	N03AG01	1500	23.88
1975	Clonazepam	(CLZP)	N03AE01	8	12.13
1990[2]	Vigabatrin	(VGB)	NO3AG04	2000	78.55
1991	Oxcarbazepine	(OXC)	N03AF02	1000	37.43
1995	Lamotrigine	(LTG)	N03AX09	300	100.12
1996	Felbamate	(FBM)	N03AX10	2400	198.43
1999	Topiramate	(TPM)	N03AX11	300	125.72
1999	Gabapentin	(GBP)	N03AX12	1800	109.13
2001	Levetiracetam	(LVT)	N03AX14	2000	143

[1] Cost in Euros for 30 DDD (monthly total cost for average adult dose based on most frequently used oral dosage form). Source: GIP database

[2] In this article, antiepileptic drugs introduced from 1990 onwards are regarded as new AEDs.

the pharmacotherapeutic arsenal: carbamazepine, phenobarbital, phenytoin and valproate. However, 30 to 40% of the patients do not become seizure–free with these conventional drugs. Furthermore, their usefulness is limited by a relatively high frequency of side effects (1,2).

The introduction of several new antiepileptic drugs in the last decade has therefore been a welcome expansion of the treatment options. The new antiepileptic drugs are 5 to 20 times more expensive than the conventional antiepileptic drugs (table 1). This is worth noting, as the cost of pharmacotherapy represents a main cost–increasing factor in epilepsy care (3). Even in studies initiated before the arrival of new antiepileptic drugs, drug costs accounted up to 40% of the immediate medical costs (3,4).

Lamotrigine was registered in the Netherlands in 1995. The introduction of lamotrigine was followed by a period of prolonged compassionate use, as it became fully reimbursed only after the establishment of a guideline for restrictive use by the Dutch Health Care Insurance Board in August 1997 (5). The relatively high acquisition cost of lamotrigine, and a lack of clinical documentation in favour of lamotrigine in treating epilepsy, were the main criteria for the Health Care Insurance Board to issue this prescribing guideline. The Lamotrigine Prescription Guideline allows full reimbursement of lamotrigine only for patients diagnosed with epilepsy with whom at least three treatment strategies with conventional antiepileptic drugs had failed. This guideline also applies to new antiepileptic drugs introduced after lamotrigine. These drugs were therefore reimbursed shortly after their introduction. The aim of the present study is to estimate the impact new antiepileptic drugs have on volume and cost of antiepileptic

drugs in the Netherlands. In order to study the utilisation of antiepileptic drugs in the Netherlands, data were obtained from the Dutch Drug Information Project (GIP).

METHODS

Data on drug utilisation

The GIP is a unit of the Dutch Health Care Insurance Board, whose goal is to collect and interpret information on drug use in the Netherlands. The GIP database contains complete information on extramurally prescribed, reimbursed drugs dispensed by pharmacists and general practitioners with in-house pharmacies. Ten selected health insurance companies provide the data. This data refers to the 5.6 million inhabitants who are covered by the Dutch National Health Service, which amounts to about 55% of all inhabitants thus covered. The data is extrapolated to the entire insured population, i.e. those either with National Health Service or with private health insurance. For this extrapolation, coefficients have been ascribed to each collaborating health insurance company, based on patient characteristics and consumption differences between those covered under the compulsory National Health Scheme and privately insured patients. Each prescription in the GIP database contains information on the number of filled drug units, the number of dispensed defined daily doses, gender and age of the patients and the type of prescribing physician. All prescription drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification (6).

Information was obtained from the GIP database on all dispensed antiepileptic drugs (ATC-code: N03, table 1) in the period from 1995 to 2001. The following drugs marketed in the Netherlands after 1990 were classified as new antiepileptic drugs: felbamate, gabapentin, lamotrigine, oxcarbazepine, topiramate and vigabatrin. All other drugs with ATC-code NO3 were classified as conventional antiepileptic drugs.

Statistics and definitions

The statistics on drug consumption and cost are presented as an average of the total insured population. Drug consumption is expressed as the number of defined daily doses (DDD) per 1,000 insured persons per day. The DDD is a technical unit of measurement, usually based on the average dosage per day for the main indication in adult patients (6).

The cost of pharmaceutical care is presented as a total cost. The total cost can be broken down into two major components: the prescription drug cost and the dispensing fee. The cost is expressed in euros (€; exchange rate on 4 November 2003: EUR 1 = USD 1.15 or GBP 0.69).

RESULTS

Consumption

Table 2 presents the utilisation data of antiepileptic drugs in the Netherlands during the period 1995 to 2001 in DDD per 1,000 insured persons per day. The consumption of antiepileptic drugs increased from 5.4 DDD per 1,000 insured persons per day in 1995 to 7.0 DDD in 2001. The conventional antiepileptic drugs carbamazepine, phenytoin and valproate were the most commonly prescribed drugs throughout the study period. The use of phenytoin decreased, however, from 1.28 DDD per 1,000 insured persons per day in 1995 to 0.96 in 2001.

New antiepileptic drugs account for 60% of this increase, with 0.96 DDD per 1,000 insured persons per day. The volume share of new antiepileptic drugs increased from 0.27 DDD per 1,000 insured persons per day (5%) in 1995 to 1.2 DDD (17.5%) in 2001.

For the first years after the introduction of lamotrigine, its volume of consumption remained low, at 0.04 DDD per 1,000 insured persons per day in 1997. After 1998, lamotrigine started to gain market share; in 2001, the volume share was 6%. Another strong volume increase in antiepileptic drugs was seen when gabapentin reached 0.25 DDD per 1,000 insured persons per day in the second year after its introduction.

In 2001, gabapentin, lamotrigine and oxcarbazepine were the most frequently used new antiepileptic drugs, and their consumption is still increasing. Compared with these three drugs, the consumption of topiramate remained relatively low at 0.08 DDD per 1,000 insured persons per day in 2001. The use of vigabatrin decreased from 0.18 DDD per 1,000 insured persons per day in 1995 to 0.05 in 2001. After the introduction of felbamate in 1996, its consumption volume remained below 0.01 DDD per 1,000 insured persons per day.

Cost

In 1995, the total cost of pharmaceutical care amounted to € 21.5 million, of which conventional antiepileptic drugs accounted for 83% (€ 17.8 million). In 2001, the total cost more than doubled when € 47 million was spent on antiepileptic drugs in pharmaceutical care. A major share (80%) of this € 25.5 million cost increase is accounted for by the introduction of new antiepileptic drugs. The market share of the new antiepileptic drugs increased from € 3.8 million in 1995 (17%) to € 24.2 million (52%) in 2001. During the study period, the cost per DDD went up from € 0.7 per DDD in the period 1995–1997 to € 1.2 per DDD in 2000, a 63% increase. As figure 1 shows, until 1997 the development in costs trailed behind the volume development; after 1997, the cost of antiepileptic drugs increased strongly in relation to consumption. Both 1998 and 2001 showed peak increases in the cost of pharmaceutical care, with relative increases of 123% in both years. The first peak increase coincided with the changed reimbursement policy regarding lamotrigine. In 1998, when € 4.1 million were spent on lamotrigine,

Table 2. Utilisation of antiepileptic drugs in the Netherlands

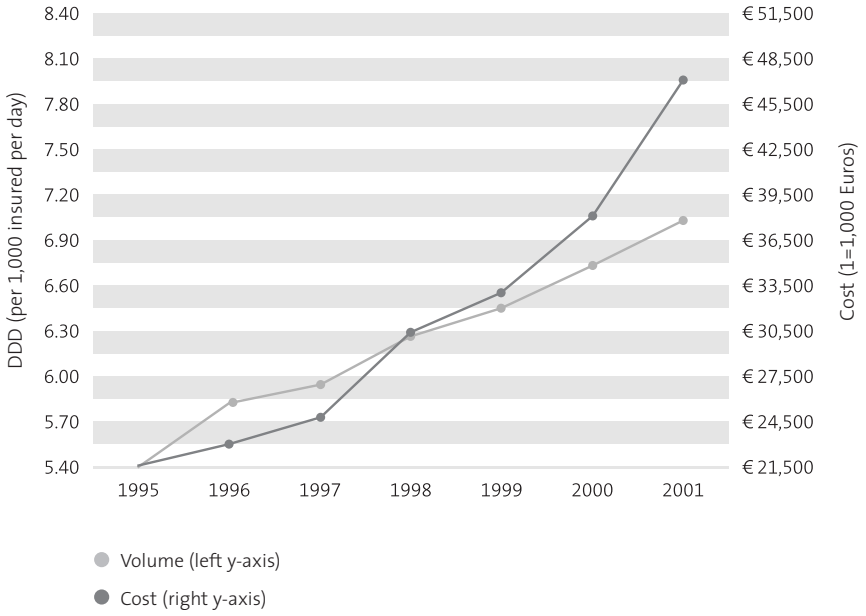
		DDD (per 1,000 insured persons per day)							Cost of pharmaceutical care (per 1,000 Euros)						
		1995	1996	1997	1998	1999	2000	2001	1995	1996	1997	1998	1999	2000	2001
Name	**ATC-code**														
old antiepileptic drugs															
phenobarbital[1]	N03AA02	0.72	0.77	0.76	0.70	0.67	0.64	0.64	603	674	654	630	686	685	674
phenytoin	N03AB02	1.28	1.25	1.20	1.19	1.16	1.13	0.96	1,287	1,250	1,244	1,254	1,340	1,316	1,312
ethosuximide	N03AD01	0.05	0.05	0.05	0.05	0.05	0.04	0.05	189	194	197	196	188	175	189
clonazepam	N03AE01	0.13	0.15	0.17	0.18	0.19	0.21	0.21	859	989	1,196	1,405	1,546	1,713	1,911
carbamazepine	N03AF01	1.69	1.79	1.75	1.80	1.84	1.86	1.87	7,671	7,471	7,229	7,584	7,849	7,794	8,061
valproic acid	N03AG01	1.25	1.44	1.54	1.68	1.80	1.96	2.06	7,163	8,133	8,73	9,373	9,507	9,929	10,566
subtotal old AEDs		**5.12**	**5.45**	**5.47**	**5.59**	**5.71**	**5.84**	**5.79**	**17,773**	**18,712**	**19,251**	**29,443**	**21,114**	**21,612**	**22,713**
new antiepileptic drugs															
oxcarbazepine	N03AF02	0.09	0.17	0.22	0.28	0.32	0.34	0.38	542	970	1,269	1,618	2,216	2,748	3,073
vigabatrine	N03AG04	0.18	0.19	0.20	0.18	0.12	0.07	0.05	3,187	3,256	3,079	2,976	2,014	1,211	909
lamotrigine	N03AX09	–	0.0	0.04	0.19	0.28	0.36	0.43	–	14	1,081	5,207	7,506	9,89	11,381
felbamate[2]	N03AX10	–	0.0	0.0	0.0	0.0	0.0	0.0	–	0	37	90	95	84	98
topiramate	N03AX11	–	–	–	–	0.01	0.06	0.08	–	–	–	–	5	1,672	2,245
gabapentin	N03AX12	–	–	–	–	–	0.03	0.25	–	–	–	–	3	816	5,766
levetiracetam	N03AX14	–	–	–	–	–	–	0.02	–	–	–	–	–	–	771
subtotal new AEDs		**0.27**	**0.36**	**0.46**	**0.65**	**0.73**	**0.88**	**1.23**	**3,729**	**5,241**	**5,466**	**9,892**	**11,838**	**16,422**	**24,242**
Total AEDs		**5.39**	**5.81**	**5.93**	**6.25**	**6.44**	**6.72**	**7.02**	**21,502**	**22,953**	**24,717**	**30,334**	**32,953**	**38,033**	**46,955**
Insured persons in the Netherlands[3]		15.22	15.31	15.36	15.44	15.50	15.60	15.68							

[1] Data of primidon, methylphenobarbital and phenobarbital presented as a combined total

[2] DDD per 1,000 insured persons per day less than 0.002

[3] 1 = 1,000,000 persons

Figure 1. Patterns in cost and volume of AEDs in the Netherlands

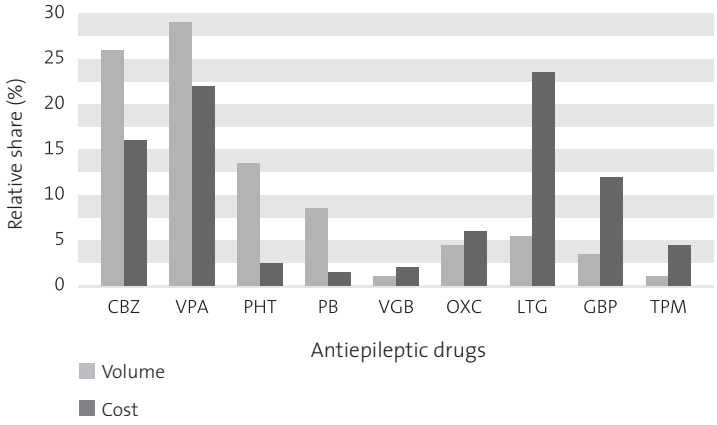


that drug accounted for 74% of the increase costs. The strong rise in gabapentin use is the major factor for the peak increase seen in 2001. The cost for gabapentin rose by € 5 million in 2001, which accounted for 56% of the total increase in pharmaceutical costs in that year. The volume and cost shares of individual antiepileptic drugs in 2001 are presented in figure 2. The overall picture is that new antiepileptic drugs have a relatively small volume share, but a comparatively high share of pharmaceutical costs. Lamotrigine, for instance, had a volume share of 6% in 2001 whereas its contribution to total pharmaceutical costs, 24%, was the highest of all antiepileptic drugs.

DISCUSSION

Drug utilisation data provides useful information to health care professionals and policy makers on different areas of interest (7). Several other researchers have also studied antiepileptic drug utilisation (8–13). Our study shares two limitations with some other studies. First, we used DDD data to determine utilisation. This does not provide insight into the percentage of people who are exposed to antiepileptic drugs, nor does it give insight into the number of new cases. Shackleton et al. and Lammers et al. collected drug–dispensing information on an individual patient level, i.e. they knew how

Figure 2. Comparison of volume and cost of AEDs in 2001



many patients used antiepileptic drugs, in which dosages these antiepileptic drugs were used and whether patients used more than one antiepileptic drug (10,11). The counting method undoubtedly supplies more specifically epidemiological information than an aggregated measure of analysis like the DDD used in this study (7).

The other limitation of this study is that the indication for which the antiepileptic drugs are prescribed is unknown. Carbamazepine and clonazepam especially are often prescribed for other indications than epilepsy. Carbamazepine and valproate are increasingly being used in the field of psychiatry. Shackleton et al. demonstrated that for almost 50% of the patients on carbamazepine monotherapy, the indication was not epilepsy (11). In several of the epidemiological studies, corrections were made for off–label use by applying a correction factor of 0.68 (8,14). For new antiepileptic drugs, the correction factor is not yet known, but it is likely that there is off–label use of these compounds as well. The effectiveness of gabapentin and lamotrigine is being assessed for several other diseases, mainly bipolar disorder and neuralgic pain (15–19). Despite these limitations, the present study still allows a comparison to be made between the prescribing of different drugs within one class and the related cost consequences. The GIP database is based on the computerised registration of prescription drugs by several health maintenance organisations. This has the advantage of being a relatively easy, inexpensive and rapid way to collect information on drug use for a large number of patients (20). Our study uses a much larger database than other studies did.

The Lamotrigine Prescription Guideline confined the use of the drug to the treatment of patients with refractory epilepsy only. This guideline was issued almost two years after the registration of lamotrigine in the Netherlands, which explains the low volume share of lamotrigine in the first years after registration. Only after the reimbursement

settlement in August 1997 did the volume share start to increase. Nowadays, lamotrigine is the most frequently prescribed new AED in the Netherlands.

The conventional antiepileptic drugs, in particular carbamazepine and valproate, are still the most frequently prescribed drugs. Their volume share continues to increase, which may also be due to off–label use. In 2001, the new antiepileptic drugs accounted for 18% of the use in antiepileptic drugs. Despite this still modest volume share, the impact of the new antiepileptic drugs on the development of costs of pharmaceutical care seems large. Over the study period, the cost of pharmaceutical care more than doubled, to € 47 million in 2001. The market share of new antiepileptic drugs soared from 17% in 1995 to 52% in 2001. Lamotrigine has the highest share of pharmaceutical care costs at € 11 million in 2001 (24%). A similar pattern in drug sales was seen in the United Kingdom, where the introduction of new antiepileptic drugs led to a twofold increase in costs of AED prescriptions in the period 1992 to 1997 (3).

At present, the utilisation of new antiepileptic drugs can still be described as modest, considering that around a third of the patients have refractory epilepsy (11). This may be due to an effective implementation of the Lamotrigine Prescription Guideline among prescribing physicians, but this has not been assessed. There are also other factors that probably contribute to the modest utilisation volume of new antiepileptic drugs. Petri and Urquhart described a so–called channelling phenomenon, which means prescribing new drugs to a selected group of patients (21). In epilepsy treatment, channelling would consist of using new antiepileptic drugs for intractable patients only, irrespective of a guideline. Furthermore, physicians may hesitate to prescribe new antiepileptic drugs soon after registration because not all relevant data on safety is available at the moment. Felbamate and vigabatrin are cases in point. Both drugs were introduced as promising new antiepileptic drugs, but as table 2 shows, these drugs are now seldom prescribed. These two drugs are associated with severe, idiosyncratic adverse effects that became apparent only several years after the drugs had been registered (22,23).

When considering the cost consequences presented in this paper, it is important to ask whether the present positioning of the new antiepileptic drugs will be subject to change in the near future. Data is emerging on the efficacy and tolerability of new antiepileptic drugs in patients with newly diagnosed epilepsy (24–29). The main advantage of the new antiepileptic drugs over conventional drugs like carbamazepine and phenytoin seems to be a favourable tolerability profile, which leads to fewer treatment failures. In the case of lamotrigine, its better tolerability profile resulted in a higher quality of life for patients treated with the drug, compared with those treated with carbamazepine or phenytoin (27,30). The results of these monotherapy trials may contribute to a more widespread use of new antiepileptic drugs earlier in the treatment and thus to their being employed as first–line treatment for newly diagnosed epilepsy. Physicians may decide to switch from conventional antiepileptic drugs as first–line treatment options to the new alternatives based on the lower number of treatment

failures. The utilisation of phenytoin is decreasing (table 2), possibly because physicians are changing their treatment preference towards new antiepileptic drugs with fewer side-effects.

Conclusion

Unbridled use of new antiepileptic drugs will inevitably impose a tremendous burden on the healthcare budget. A well-regulated healthcare environment will increasingly mandate a demonstration of value for money, defined in terms of measurable health and/or financial outcome for a given pharmacotherapeutic option. Selection criteria for the rational use and positioning of new antiepileptic drugs are needed, criteria which should be based on effectiveness and cost-benefit data derived from real-life use. Without data on population-based effectiveness of new antiepileptic drugs, plan payers, like the Dutch Health Care Insurance Board, will remain wary about paying for new drugs or reconsidering the positioning of these drugs. Drug utilisation studies should be included in the ways of finding criteria that attribute to a rational positioning of the new antiepileptics and in demonstrating that new antiepileptic drugs, when effective, will almost always justify their cost.

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Diffusion of the new antiepileptic drug lamotrigine in Dutch clinical practice

2.3

ABSTRACT

Objective

Lamotrigine is one of the recently introduced antiepileptic drugs licensed in the Netherlands in 1995. The objective of this study was to examine the diffusion of lamotrigine into clinical practice. Three different aspects of this diffusion process were examined: incidence of use, patient characteristics and changes in prescription patterns in the first 5 years following its introduction.

Methods

A retrospective follow–up study has been conducted using drug prescription data from the database of the Dutch Drug Information Project (GIP–database). Patients were included who started with lamotrigine, carbamazepine, phenytoin or valproate in the period of January 1996 to December 2000. Incidence of use was calculated for the four drugs. Multiple logistic regression analysis was used to determine differences in baseline characteristics. Chi–square test was used to analyse changes in the usage patterns of lamotrigine.

Results

The study population consisted of a total of 29,718 patients who were prescribed carbamazepine, phenytoin, valproate or lamotrigine for the first time in the study period. Carbamazepine and valproate accounted for the majority of all new prescriptions; the incidence of lamotrigine use remained stable with 4.4 patients per 100,000 per year. Baseline characteristics of lamotrigine differed, depending on the patient's age and gender compared to the conventional antiepileptic drugs. In a large majority of cases lamotrigine was used as a second–line or third–line antiepileptic drug. Physicians prescribing lamotrigine were predominantly neurologists, in contrast to prescribers of conventional antiepileptic drugs. The prevalence of psychotropic medication and migraine–abortive drugs was significantly lower in users of lamotrigine compared to users of conventional antiepileptic drugs. During follow–up several significant trends were noticed in the prescribing of lamotrigine with regard to age groups, gender, antiepileptic history and off–label use.

Discussion

Lamotrigine is prescribed to a population different from that using conventional antiepileptic drugs. The uptake of lamotrigine in clinical practice is slow, for reasons probably related to characteristics of the drug itself and the prescribers. During the observation period, lamotrigine diffused gradually towards more first–line use as an antiepileptic drug and more off–label use.

INTRODUCTION

The field of antiepileptic drug therapy is dominated by conventional drugs, such as phenytoin (introduced in 1938), carbamazepine (1964) and valproate (1971) (1). As a substantial proportion of the patients is not controlled optimally or suffers from bothersome or clinically severe side–effects while using conventional antiepileptic drugs (2), there remains a clear need for new drugs. Lamotrigine is one of the new treatment options that has been introduced in the past decade. On the basis of results from placebo–controlled trials, lamotrigine received regulatory approval in the Netherlands for indication in 1995 as an add–on drug in patients with refractory, localisation–related epilepsy. The reimbursement of the drug was not immediately approved by the Dutch Health Care Insurance Board because of its relatively high cost compared to conventional antiepileptic drugs, and also because of a lack of favourable clinical documentation on lamotrigine (as head–to–head comparisons with other antiepileptic drugs were lacking). In August 1997, the Health Care Insurance Board decided that the reimbursement of lamotrigine should be restricted to the initial indication, i.e. add–on therapy for patients with refractory epilepsy. A prescription guideline, the first in the Netherlands, was issued by the Health Care Insurance Board and distributed among Dutch neurologists (but not other physicians) to ensure the restricted use of lamotrigine. It is to be expected, however, that once physicians become familiar with the use and safety of a new antiepileptic drug, the drug will be prescribed for a broader range of indications, e.g. to patients with less severe epilepsy or to patients from other age groups than those included in the initial trials. Still little is known about this process of diffusion of new drugs in daily practice. Most available theoretical frameworks rely on Rogers' diffusion of innovations theory (3–5). Rogers defined diffusion as the process by which an innovation disseminates through certain channels over time among members of a social system (3). In the decision to prescribe a new drug, doctors have to strike a balance between possible benefits and risks. Because new drugs are generally more expensive than established drugs, doctors also have to make this judgement in the wider context of a health service with a limited budget (6). Within this context, health care providers and formulary decision–makers, too, often evaluate newly introduced drugs. Knowledge of the diffusion process would help doctors as well as policy makers in the interpretation of aspects such as effectiveness and economic outcomes of new drugs. The objective of this study was to examine the diffusion of lamotrigine after it became reimbursed in the Netherlands, using a large prescription database over the period from 1996 – 2000. Prescribing trends, usage patterns, and baseline characteristics of patients in a cohort of lamotrigine patients were compared with those of a cohort of patients using the conventional antiepileptic drugs carbamazepine, phenytoin and valproate.

METHODS

Setting

The prescription data for this study was obtained from the GIP–database. This is a project run by the Dutch Health Care Insurance Board, an independent advisory and supervisory body in the field of social health insurance. The GIP–database contains data from all extramurally prescribed drugs that are dispensed by pharmacists and general practitioners with an in–house pharmacy and are reimbursed by the health insurance funds under the Health Insurance Act. The data was provided by ten health insurance funds and concerns 5.6 million compulsorily insured in 2000, which is about 55% of all compulsorily insured Dutch persons. This sample is representative for the distribution by age and gender of all persons compulsorily insured in the Netherlands.

For each prescription in the GIP–database, retrievable information covers the following domains: patient (gender, age and unique anonymous identification number); prescription (trade name, ATC code, dispensing date, dispensed amount and prescribed dose); and prescriber (general practitioner or specialist). The GIP–database does not provide information concerning indications for use of the medicines nor the complete registration of non–prescription medicines.

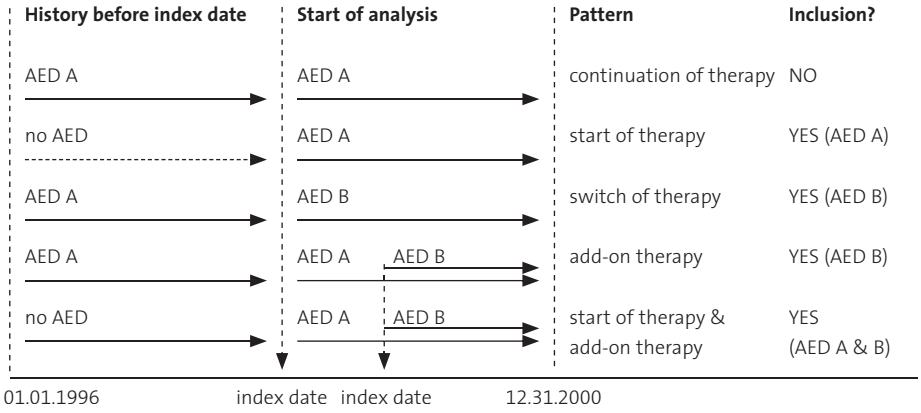
Study population

We collected prescription data from the GIP database of all patients who received at least one prescription in the period January 1 1996 – December 31 2000 for lamotrigine and/or one of the three most frequently prescribed antiepileptic drugs in the Netherlands (i.e. carbamazepine, phenytoin or valproate; n = 98,043). Other antiepileptic drugs in the Netherlands (i.e. clonazepam, ethosuximide, felbamate, oxcarbazepine, phenobarbital and vigabatrin) represent a combined market share of less than 15% and were not considered in this study. The date of first prescription of one of the four antiepileptic drugs was defined as the index date. First–time use was defined as a prescription for one of these four antiepileptic drugs written during the study period, with no prescription for the same drug having been during the twelve months before the index date. Only first–time users were included in this study (n = 37,695). Due to the selection criteria, these were only first–time users from January 1997 onwards.

In the Netherlands drugs are dispensed for a maximum of three months. In order to prevent the occurrence of information gaps, patients were included only if the period between two subsequent prescriptions (any drug) was less than 180 days (n = 32,206).

Thus, the final study population included only new users of one of the four antiepileptic drugs: either patients who did not receive any antiepileptic drug during the twelve months before the index date, or patients who received one or more other antiepileptic drugs before the index date (figure 1).

Figure 1. Study population



The study population included only new users of a specific AED (e.g. AED A or AED B) during January 1996 until December 2000. As a consequence of the long time-frame one patient could be a new user of more than one AED.

Analysis of the diffusion process

The diffusion process of lamotrigine was characterised by analysing different aspects of the prescription pattern. First, the market share of lamotrigine was compared to that of the three conventional antiepileptic drugs. Market share of the four antiepileptic drugs was calculated as the number of first–time users of the antiepileptic drug during the study period divided by the source population in the GIP database.

As a second aspect of the diffusion process, differences in the prevalence of baseline characteristics in the lamotrigine cohort and the cohort of patients receiving the conventional antiepileptic drugs (reference group) were compared. Crude prevalence odds ratios were calculated using multiple logistic regression and were presented with a 95% CI. The whole group of users of conventional antiepileptic drugs was taken as reference, instead of users of separate conventional antiepileptic drugs, because the combined group was considered to be more representative of the entire population using antiepileptic drugs. In the comparisons between new users of lamotrigine and the reference group the following characteristics were evaluated:

- age (on the index date) and gender;
- type of prescriber: general practitioner, neurologist, psychiatrist or other;
- prescription of different antiepileptic drugs during the twelve months before the index date. The prior use of antiepileptic drugs, and especially that of vigabatrin, was used as a marker for refractory epilepsy;
- prescription of psychotropic agents (antidepressants, antipsychotics, lithium salts) and abortive migraine medication during the twelve months before the index

date. The use of these drugs was used as a marker for off-label use (e.g. for bipolar depression, migraine) of lamotrigine.

As a consequence of the long follow–up period, patients could be a first–time user of more than one antiepileptic drug (as shown in figure 1). For the statistical methods used, independent observations are required, which is not the case if a patient contributed more than one observation. Therefore, an analysis was also performed that was restricted to only one new use (chosen randomly) for each user with multiple new uses. This did not change the estimates.

A third aspect of the diffusion process was the analysis of any changes in the population that used lamotrigine throughout the study period. In order to find out if lamotrigine treatment reached a more heterogeneous population than the one considered for inclusion in the initial add–on randomised controlled trials (7,8), trends in the following baseline characteristics were evaluated:

- increased prevalence of lamotrigine in patients outside the age category 18 – 65;
- increased prevalence of lamotrigine in patients without a history of antiepileptic drug use;
- increased prevalence of lamotrigine in patients with either lithium or abortive migraine medication in their history.

The trend analyses also evaluated if the prescription patterns regarding gender changed through time. For these analyses the relative risks (RR) per period of three months were calculated using the first three months after the start of reimbursement of lamotrigine as reference. The Chi–square test was applied to statistically describe trends in prescribing from 1997 to 2000.

RESULTS

A total of 29,718 patients were identified who received a prescription of carbamazepine, phenytoin, valproate or lamotrigine for the first time during the study period. These patients accounted for a total of 32,206 new uses of antiepileptic drugs. The development in market share is presented in figure 2. Carbamazepine and valproate accounted for the majority of all new prescriptions (52% and 29%, respectively). After reimbursement settlement (August 1997), the market share of lamotrigine rose quickly to approximately 9 patients per 100,000 persons insured per year. Initially, the market share of lamotrigine exceeded that of phenytoin (approximately 7 patients per 100,000), but from 1998 onwards the market share of lamotrigine levelled off to approximately 4.4 patients per 100,000 per year. On average, the market share of lamotrigine was less than 10%; within the group of neurologists, the market share reached 16%.

Figure 2. Incidence of antiepileptic drugs in the Netherlands

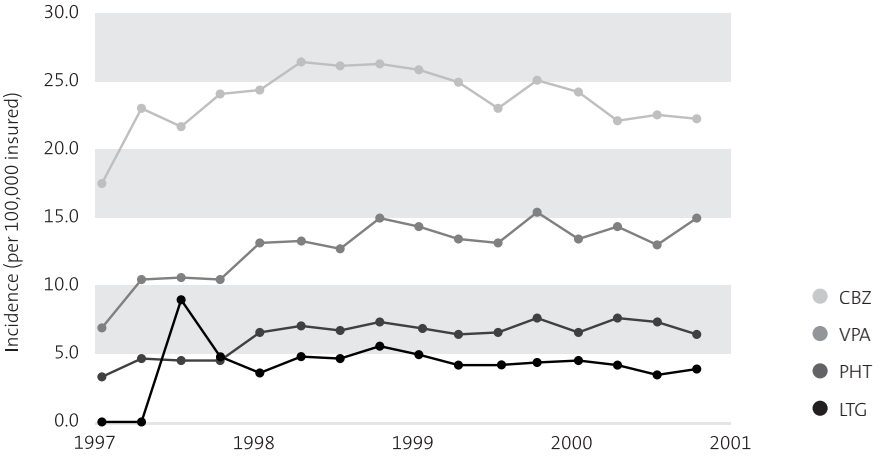


Table 1 shows the characteristics of the patients stratified according to the antiepileptic drug treatment started with at the index date. Overall, 60% of the patients were women, the median age was 52. A majority of patients (76%) had no history of antiepileptic drugs in the year before the index date. A high prevalence of psychotropic drugs was registered, especially benzodiazepines (47%) and antidepressants (24%). Differences in baseline characteristics of the lamotrigine group and the reference group are presented in table 2. Lamotrigine users were significantly younger than users of one of the conventional antiepileptic drugs ($OR_{0-17\ years}$ 2.8; 95%CI 2.5 – 3.1), and more often male than female (OR 1.4; 95%CI 1.3 – 1.5). Lamotrigine patients had more frequently used one or more antiepileptic drug prior to the index date when compared to users of one of the conventional antiepileptic drugs (OR 35.5; 95%CI 31.6 – 39.9). Prior use of vigabatrin was significantly more prevalent in the lamotrigine group (OR 25.5; 95%CI 21.9 – 29.7). Prescribers of lamotrigine were more often neurologists (OR 2.8; 95%CI 2.6 – 3.0). In addition, the prevalence of psychotropic medication and migraine–aborting drugs was significantly lower with users of lamotrigine than with users of conventional antiepileptic drugs.

Several significant changes were observed in the type of patients receiving lamotrigine during the first years after its introduction (figure 3). The ratio of age categories changed; the RR for patients outside of the age category 18–65 (included in the initial randomised controlled trials) increased to 3.0 at the end of the study period (p–value for trend < 0.01). The number of patients in the age category 18–65 fell from 86% in 1997 to 68% in 2000. The RR for patients without a history of use of another antiepileptic drug increased to 5.2 (p–value for trend < 0.01). The number of patients

Table 1. Baseline characteristics of the study population

Characteristics, N(%)		Comparator group (n = 29,262)		
	LTG (n = 2,944)	CBZ (n = 16,845)	VPA (n = 9,267)	PHT (n = 3,150)
Gender				
Male	1,377 (46.8)	6,249 (37.1)	3,748 (40.4)	1,433 (45.5)
Female	1,567 (53.2)	10,596 (62.9)	5,519 (59.6)	1,717 (54.5)
Age				
0–17 years	483 (16.4)	497 (2.9)	907 (9.8)	58 (1.8)
18–64 years	2,164 (73.5)	10,304 (61.2)	6,123 (66.1)	1,665 (52.9)
≥ 65 years	297 (10.1)	6,044 (35.9)	2,237 (24.1)	1,427 (45.3)
Prior use of antiepileptic drugs				
None	341 (11.6)	14,779 (87.7)	7,094 (76.6)	2,210 (70.2)
One	855 (29.0)	1,679 (10.0)	1,631 (17.6)	637 (20.2)
Two	1,069 (36.3)	304 (1.8)	400 (4.3)	206 (6.5)
Three or more	679 (23.1)	83 (0.5)	142 (1.5)	97 (3.1)
Vigabatrin	555 (18.9)	77 (0.5)	120 (1.3)	67 (2.1)
Prescriber				
General Practitioner	506 (17.2)	9,489 (56.3)	2,241 (24.2)	1,051 (33.4)
Neurologist	1,456 (49.4)	2,899 (17.2)	3,422 (36.9)	1,283 (40.7)
Psychiatrist	70 (2.4)	704 (4.2)	818 (8.8)	15 (0.5)
Other	912 (31.0)	3,753 (22.3)	2,786 (30.1)	801 (25.4)
Prior use of comedication				
Antidepressants	312 (10.6)	4,599 (27.3)	2,273 (24.5)	535 (17.0)
Antipsychotics	188 (6.4)	1,427 (8.5)	1,538 (16.6)	188 (6.0)
Benzodiazepines	1,146 (38.9)	8,227 (48.8)	4,235 (45.7)	1,443 (45.8)
Lithium	65 (2.2)	591 (3.5)	735 (7.9)	11 (0.3)
Migraine abortive drugs	85 (2.9)	734 (4.4)	1,256 (13.6)	89 (2.8)

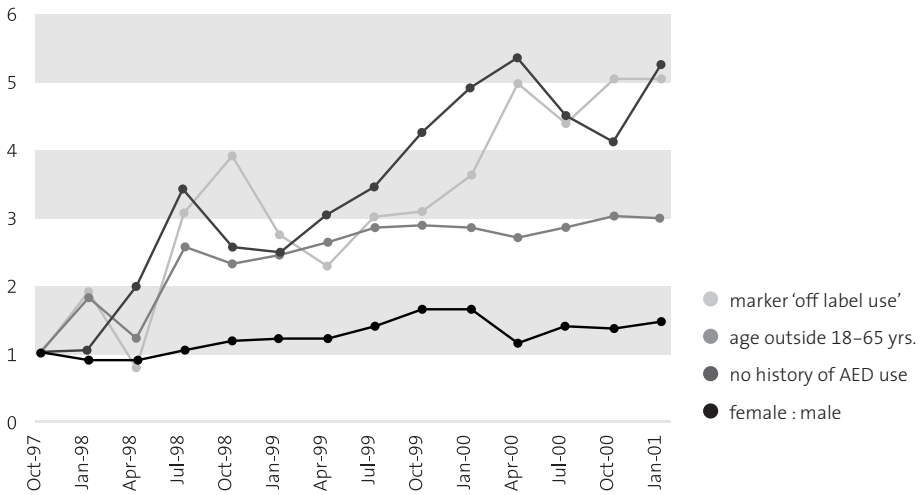
using lamotrigine without prior use of any antiepileptic drug increased from 3% in 1997 to 16% in 2000. Overall, the mean number of antiepileptic drugs prior to the index date of lamotrigine dropped from 2.2 in 1997 to 1.5 in 2000. The RR for markers of off–label use increased to 5.0 (p–value for trend < 0.01). Over the study period, a significant increase in the number of prescriptions for women was noticed: the RR increased to 1.5 (p–value for trend < 0.01). Differences in the prescription patterns of the conventional antiepileptic drugs were analysed in a similar way; however, no significant changes were observed for any of the baseline characteristics. The same analyses were applied for the reference group; the RRs for the characteristics mentioned above did not change significantly.

Table 2. Characteristics of patients starting with lamotrigine compared to those starting with conventional antiepileptic drugs

Characteristics	OR (95% CI)	
Gender; male	1.40	(1.27 - 1.48)
Age		
0–17 years	2.76	(2.47 - 3.09)
18–64 years	reference	
≥ 65 years	0.26	(0.23 - 0.29)
Prior use of antiepileptic drugs		
None	reference	
One	15.30	(13.43 - 17.42)
Two	82.96	(72.22 - 95.31)
Three or more	148.92	(125.60 – 176.58)
Vigabatrin[1]	25.50	(21.91 - 29.71)
Prescriber		
General Practitioner	0.21	(0.19 - 0.23)
Neurologist	reference	
Psychiatrist	0.24	(0.19 - 0.30)
Others	0.65	(0.59 - 0.71)
Prior use of comedication[1]		
Antidepressants	0.35	(0.31 - 0.39)
Antipsychotics	0.57	(0.49 - 0.66)
Benzodiazepines	0.70	(0.65 - 0.76)
Lithium	0.47	(0.37 - 0.61)
Migraine abortive drugs	0.39	(0.31 - 0.49)

Reference group =combined group of patients starting with carbamazepine, phenytoin or valproate.
OR = odds ratio. [1](presence vs. absence).

Figure 3. Trends in lamotrigine utilisation throughout the study period



DISCUSSION

Having access to a large prescription database allowed us to follow the diffusion of lamotrigine in a population–based cohort. The results of our study have shown that the uptake of lamotrigine was rather slow. After its introduction in the Netherlands, lamotrigine was prescribed to patients who had previously received other antiepileptic drugs, suggesting that it was introduced as a second–line or third–line treatment. Subsequently, the diffusion process of lamotrigine resulted in a more heterogeneous population being reached. According to Rogers, new ideas are adopted very slowly during the early stages of the diffusion process, the rate of adoption, however, increases steadily (3,4). Remarkably, after the diffusion process for lamotrigine had passed the early stages, a further increase in market share has yet to take place. Several possible barriers can be characterised that probably slowed down the uptake of lamotrigine.

a. Characteristics of the drug itself affect use. Rogers' theory states that the rate of diffusion is inversely proportional to the perceived complexity of the innovation (3). Lamotrigine is not simple to use (9). The use is hampered by a relative high incidence of idiosyncratic adverse events, predominantly rash (10,11). Review of trial data showed that severe rashes occur more often with rapid titration in pediatric patients. Valproate inhibits the metabolism of lamotrigine, and this has major clinical impact on the risk of skin reactions (9). The metabolism of lamotrigine is accelerated by enzyme-inducing antiepileptic drugs such as carbamazepine and phenytoin, necessitating higher dosage with these co-medications. The complexity of lamotrigine, i.e. the slow titration schedule and its interaction potential, will probably have caused slower diffusion, expressed in the numbers of new patients. This may possibly have been worsened by the introduction since 2000 of other new antiepileptic drugs, like gabapentin and levetiracetam, with less interaction potential and faster titration schedules than lamotrigine. It would be interesting to see whether the diffusion process of these new antiepileptic drugs was different compared to that of lamotrigine. Both gabapentin and levetiracetam, however, were not registered in the Netherlands until after 2000, so follow-up data of these drugs are absent from our database.

b. Prescriber characteristics. Individuals do not all adopt an innovation at the same time, and they can be divided into several adopter categories (innovators, early adopters, early majority, late majority and laggards) (3). The majority of physicians is considered to be conservative (late majority and laggards) regarding drug choice (6). In our study, we conclude from the differences in baseline characteristics that selective prescribing of lamotrigine to patients with more severe epilepsy has occurred. We believe that prior use of other antiepileptic drugs, and the use of vigabatrin especially, can be seen as markers for refractory epilepsy. Selective prescribing, or "channelling", is likely to occur for new representatives of a therapeutic class for which alternatives existed, as is the case for antiepileptic drugs. This is a general phenomenon, which has been demonstrated for

various drug classes, e.g. NSAIDs, antidepressants or spasmolytics (12-14). The peak in incidence noticed shortly after reimbursement approval could possibly be related to the backlog of patients with refractory epilepsy. About the introduction of lamotrigine, safety issues regarding two other new antiepileptic drugs played a part. One year after approval of felbamate, reports of aplastic anaemia began to emerge (11). Several years after the introduction of vigabatrin, evidence was produced that prolonged high-dose treatment may cause severe and symptomatic irreversible visual field constriction (9,15). The detection of such safety risks may have withheld many physician's from prescribing antiepileptic drugs that had been registered after felbamate and vigabatrin.

c. Economic aspects. The pharmaceutical cost of lamotrigine is at least a fivefold of that of conventional antiepileptic drugs. Indiscriminate switching from conventional to new antiepileptic drugs would have considerable economic implications (9). A survey among U.S. neurologists showed that neurologists recognise the need to rationalise health care and that they are willing to accept the notion that individual sacrifices can and should be made because of the finite healthcare resources (16). Increasing pressure on drug budgets will make physicians more reluctant to prescribe new drugs.What's more, the Dutch National Health Care Insurance tried, by issuing the prescription guideline for lamotrigine, to contain the cost of the drug by restricting its prescription to patients with refractory epilepsy. This may also have reduced the "trialability" of lamotrigine. "Potential adopters" want the opportunity to "test" a drug before adopting (3). The prescription guideline could have prevented this testing, although we were not able to evaluate how the guideline was adhered to in the present study.

Despite the barriers mentioned above, the diffusion of lamotrigine is still ongoing. This study shows that the cohort of lamotrigine users is subject to change. Gradually, the baseline characteristics of the patients start to drift away from those of the patients in the initial, add–on regulatory trials. From 1997 to 2000, lamotrigine gradually became an antiepileptic drug of first and second choice, and was increasingly being given to children and elderly persons. It is well–known that the publication of new, high–level evidence (i.e. randomised controlled trials) influences prescription patterns (17). Randomised trials comparing lamotrigine to carbamazepine, phenytoin and valproate in patients with newly diagnosed epilepsy are available in medical literature (18–21). Broadly speaking, these trials showed that lamotrigine cannot claim greater efficacy than the conventional antiepileptic drugs but that the drug seemed to be tolerated better than its comparators, with fewer withdrawals due to adverse events. A similar result emerged from a trial comparing lamotrigine and carbamazepine in elderly patients (over 65 years of age) with newly–diagnosed epilepsy (22). Trials and observational studies assessing lamotrigine in the treatment of childhood epilepsy syndromes also became available. This is likely to be an important factor explaining the overall trend towards more use of lamotrigine for the young, as carbamazepine and phenytoin are not indicated in

the treatment of the idiopathic generalised epilepsy syndromes. Trial data on the effectiveness of lamotrigine in the treatment of other diseases than epilepsy has also started to emerge (23–26). We noticed a strong increase in markers for off–label use. Our data suggests that there is an increased use of lamotrigine for second–line treatment of bipolar disorder (markers: lithium and antidepressants); neuropathic pain (marker: antidepressants) and migraine (marker: abortive migraine drugs).

Compared to the conventional antiepileptic drugs, lamotrigine has been positioned as a better alternative for women of childbearing age, which may explain the increased prevalence in women. There are several aspects that make lamotrigine favourable for this group of patients. First, pregnancy data on lamotrigine increases and the drug does not seem to have major teratogenic effects (27). Given the known effects of the conventional antiepileptic drugs, this may possibly explain the increase seen. Second, there is a controversy regarding the question whether the use of valproate is associated with a higher incidence of polycystic ovary syndrome (PCOS) (28,29). Herzog and Schacter conclude that, despite limitations in studies reporting an association between the use of valproate and occurrence of PCOS, the evidence cannot be entirely dismissed (30). As valproate also has teratogenic effects, it may be concluded that it is less suitable for women of childbearing age. Lamotrigine has been positioned as a better alternative for this group. Third, lamotrigine lacks an enzyme–inducing capacity and does not reduce the effect of oral contraceptives (whereas carbamazepine and phenytoin do). More recently, however, a relevant interaction between lamotrigine and oral contraceptives became known (31).

The changing baseline characteristics shown in figure 3 make it clear that there is a gap between the information available from the initial randomised controlled trials and the use of lamotrigine in the real world of medicine. These changes are relevant to issues like rational drug therapy, effectiveness and safety in a population–based setting. This supports post–marketing surveillance studies addressing these issues (32). The results of this study should be interpreted in the light of its limitations. A first limitation of our study is the lack of additional medical information, most importantly the indications of use. It is common knowledge that antiepileptic drugs are used for other indications than epilepsy. However, to what extent, depends on the individual antiepileptic drug (33). Using a Dutch prescription database (PHARMO), Shackleton et al. demonstrated that epilepsy was present in 58% of patients using a single antiepileptic drug, and epilepsy prevalence was 93% in patients using more than one antiepileptic drug (33). Carbamazepine was more often used for other indications than the other conventional antiepileptic drugs. We believe that, by using a combined reference group, we are comparing lamotrigine to a population–based use of conventional antiepileptic drugs (i.e. use of these drugs for epilepsy and other indications as prescribed by various types of physicians). We had to use surrogate markers, however, to illustrate off–label use of lamotrigine. The prevalence of a marker in an individual patient will not always mean

that off–label use is the case, for some misclassification has certainly occurred.

Furthermore, the GIP database comprises prescription data of the compulsorily insured patients in the Netherlands. It might be argued whether the results are also representative for the higher socio–economic classes, which are not covered by the national health insurance system. However, as there are no reimbursement limitations for antiepileptic drugs in both the national health insurance system and the private insurance companies, difference between socio–economic classes are not expected. Another limitation is that we were not able to evaluate other relevant characteristics that enhanced diffusion, such as the physician's attitude towards new drugs like lamotrigine, or the impact of drug marketing by the pharmaceutical company. The latter aspect may also be a explanation for the increased use of lamotrigine for women; however, we were not able to evaluate this.

Our conclusion is that there are a multitude of factors influencing the diffusion of lamotrigine into daily practice. Starting in a selected group of patients with severe epilepsy, the drug gradually diffuses to a much more heterogeneous population. Understanding the process of diffusion is important in the evaluation of the place in therapy of lamotrigine, its effectiveness in real life and its cost consequences.

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Patterns of lamotrigine use in daily clinical practice during the first five years after introduction in the Netherlands

2.4

ABSTRACT

Objective

Follow–up data on the long–term effectiveness (efficacy and tolerability) of lamotrigine are limited. A useful though crude measure for effectiveness in daily clinical practice is the treatment retention rate determined from drug dispensing data. This study describes the baseline characteristics, the usage patterns and the retention rate of this antiepileptic drug in a population–based cohort of lamotrigine users in the Netherlands during the first five years after its registration in 1995. Data from this cohort are compared with those from the initial randomised clinical trials (RCTs) in patients with refractory epilepsy.

Methods

This retrospective cohort study used dispensing data from community pharmacies. Baseline characteristics and usage patterns were evaluated for first time users of lamotrigine in this study. Usage patterns were characterised as continued, add–on or discontinued use during the patient observation time window. Cox regression analysis was used to explore possible relationships between baseline characteristics and specific usage patterns defined. The baseline characteristics and discontinuation rates in this cohort study were compared with randomised controlled trial data reported in medical literature.

Results

A total of 3,598 lamotrigine users were identified. The mean age of the population was 39 years and 54% were female. On average, patients used two other antiepileptic drugs at the start of lamotrigine therapy and approximately 6% of the patients had no history of prior antiepileptic drug use. The discontinuation rate was 25% after one year, and approximately 32% at the end of the 5–year study. Addition of another drug or discontinuation was seen in more than half of the population three years after the start of therapy. Concurrent use of valproic acid was associated with a better retention rate. Absence of antiepileptic drug history, use of antidepressants, or use of migraine abortive drugs resulted in an increased likelihood of discontinuing lamotrigine. The population from randomised controlled trials differed from the study cohort with respect to age, concurrent use of antiepileptic drugs and length of follow–up.

Discussion

Data from randomised controlled trials cannot easily be extrapolated to daily clinical practice. In this large, observational study, lamotrigine therapy failed in a considerable number of patients, although the mean retention rate was better than previously reported by others. Population–based linkage of health care records can be used to further clarify the effectiveness of lamotrigine.

INTRODUCTION

Lamotrigine was introduced in the Netherlands in 1995, based on data from clinical trials regarding its efficacy, tolerability and safety. In add–on trials involving patients with intractable epilepsy, lamotrigine reduced seizure frequency by more than 50% in approximately 30% of patients (1–3). However, clinical trials do not mirror daily practice, as in trials the effects of the drug are examined (a): for a limited period of time; (b): under well–controlled conditions and (c): in a homogeneous, though highly selected, group of patients (4,5). This may affect the generalisability of findings from clinical trials with regard to efficacy, tolerability and safety to daily clinical practice and pleas for observational research within the setting of daily clinical practice.

A useful though crude measure of effectiveness in large observational studies is the retention time using drug–dispensing data. Effectiveness is an outcome measure, which encompasses both efficacy and tolerability (6). This study focused on the retention time on lamotrigine and on patterns of the drug's use in the Dutch community. By using dispensing data, we identified lamotrigine users during the first five years after its introduction. The objective of the present study is to describe baseline characteristics, and compare these characteristics with those from the initial clinical trials of lamotrigine in patients with refractory epilepsy.

METHODS

Data collection and source population

There is a high level of agreement between automated pharmacy data and self–reported drug use, especially for drugs used chronically (7,8). Analysing computerised records of prescriptions actually filled, thus makes it possible to collect information on drug use for a large number of patients (9,10).

This retrospective cohort study used prescription data from community pharmacies in the Netherlands. A total of 1428 (90%) pharmacies out of 1586 Dutch pharmacies in January 2001 received a request for anonymous data of all patients to whom lamotrigine was dispensed during the observation period. The selected pharmacies used one of the

Table 1. Application of inclusion criteria to the initial patient population

Inclusion criteria	Number of patients excluded	Remaining study population
Initial population	–	6,544
A minimum of 1 year drug history before index date*	1,786	4,758
Less than 180 days between two successive prescriptions	728	4,030
A minimum of 180 days of follow up after index date	432	3,598
Final study population	–	3,598 (55%)

*For children under two years of age an period of 180 days of drug history was required

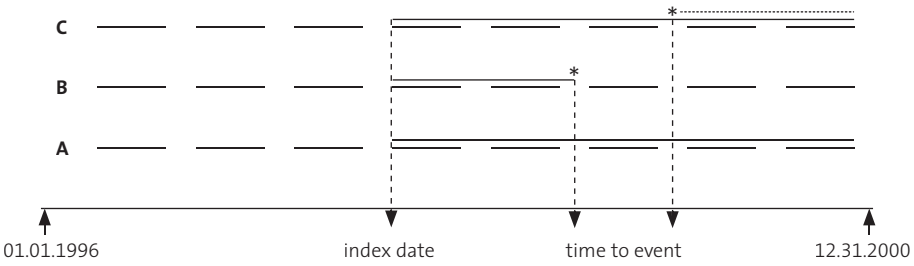
three major pharmacy computer systems in the Netherlands. These pharmacies serve an open population of approximately 13 million persons.

For each patient who filled at least one lamotrigine prescription during January 1996 to December 2000, a complete prescription drug dispensing history, covering the period 1996 – 2000, was collected by means of computerised data extraction methods. Each dispensed drug led to one electronic record containing patient information (unique though anonymous identification number, gender, date of birth and residential postal code) and information about the prescribed medicine (drug identification number, dispensing date, number of units dispensed and the prescribed daily dose). The software program Microsoft Access was used for database management, internal quality control and validation procedures. The resulting research database consisted of 6,544 patients and 660,097 prescriptions.

Study population

For the present study only those patients were included who received lamotrigine for the first time. The date of first prescription of lamotrigine was defined as the index date. To ascertain first time use, patients were required to have at least 365 days of prescription history for any medicine before the index date (180 days for children under 2 years of age). Patients who were not regular visitors of the pharmacy, defined by a time gap of more than 180 days between two successive prescriptions for whatever medication, were excluded from the analysis. Patients with a follow–up time (i.e. observation period between index date and the last ever registered prescription) of less than 180 days were also excluded. Application of these exclusion criteria resulted in a study population of 3,598 patients with 468,859 prescription records as shown in table 1.

Figure 1. Patterns of lamotrigine use



Information from all prescriptions (observation window, dashed line) and lamotrigine prescriptions (concrete line) was used to measure lamotrigine retention and to define patterns of use. A: continuation of lamotrigine; B: discontinuation of lamotrigine (more than 180 days between end date of lamotrigine and end of observation window); and C: add-on of another AED (dotted line) after the start of lamotrigine. Time to first event (either discontinuation, add-on or end of analysis) was used in statistical analyses.

DATA ANALYSIS

Baseline characteristics

Baseline characteristics of the study population that were examined included gender, age at index date and certain concomitantly used medication. For co–medication we focused on the prescription of other antiepileptic drugs, psychotropic drugs (antidepressants, antipsychotics, benzodiazepines, lithium salts) and migraine abortive drugs.

Lamotrigine patterns of use and retention rate

For each prescription, the theoretical duration of use was calculated using information on dispensing date, amount supplied and dosage regimen. The observation window for each patient was defined as the time between the date of the first prescription and the theoretical end date of the last prescription registered. Lamotrigine retention time was calculated as the sum of the theoretical duration of consecutive lamotrigine prescriptions. Patterns of use (continuation, add–on and discontinuation) were defined for cohort members, based on observation window and lamotrigine retention time (as shown in figure 1). Continuation of lamotrigine therapy was defined for patients with less than 180 days between the theoretical end date of lamotrigine and the end of the observation window. Add–on was defined if another antiepileptic drug was added to lamotrigine, without discontinuation of lamotrigine therapy. Discontinuation of lamotrigine therapy was defined for patients for whom more than 180 days elapsed between the theoretical end date of the last lamotrigine prescription refill and the end of the observation window. The baseline characteristics were explored in order to identify a possible association with the specific usage pattern defined using

Cox proportional hazard modelling. The strength of these associations was expressed by hazard ratios with 95% CI. Hazard ratios can be interpreted as relative risks (RR) in this analysis. In a subsequent analysis, we stratified patients into those who filled just one prescription and those who filled more than one lamotrigine prescription.

Comparison with reported clinical trials

We compared the data from our study with those from randomised controlled trials published in the medical literature, that examined the efficacy of lamotrigine in patients with refractory epilepsy. Data from unpublished randomised controlled trials or from trials that enrolled less than 25 patients in the lamotrigine treatment group were summarised from a meta–analysis performed by Marson et al. (3). Baseline characteristics and discontinuation rates were compared between trial population and population–based cohort.

RESULTS

Baseline characteristics

A total of 1,056 pharmacies (74% response) responded to our request to retrieve prescription data of all patients to whom lamotrigine was dispensed. The responding pharmacies covered both large and small pharmacies and both low and highly urbanised areas. In all, 3,598 new users of lamotrigine were identified during the observation period. These patients could be followed for a mean observation window of 4.6 years per patient. The corresponding baseline characteristics are shown in table 2. The mean age of the population was 39 years, and 54% was female. There were 218 (6.1%) patients not using other antiepileptic drugs on the index date. A significant trend towards an increased incidence of patients without an antiepileptic drug–history was observed from 1996–2000. On average, patients used two other antiepileptic drugs on the index date (range 0 – 8); carbamazepine and valproic acid were by far the most frequently concomitantly used other antiepileptic drugs.

Benzodiazepines (excluding clobazam, clonazepam, and diazepam) were the most prevalent concomitantly used psychotropic drugs in the year prior to the index date (26%), followed by antidepressants (10%), migraine abortive therapy (3%) and lithium (1.5%).

Retention rates and patterns of use

The mean time from the initiation of lamotrigine therapy to a change in lamotrigine therapy (discontinuation or add–on) or completion of the observation period was 1.3 years (range 17 days – 4.2 years). One year following the initiation of lamotrigine therapy approximately 25% of the study population had discontinued therapy, the

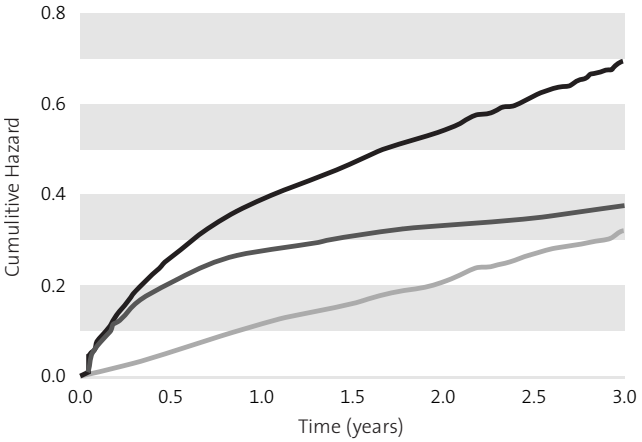
Table 2. Baseline characteristics of study population (n = 3,598)

Characteristics	Number of patients (%)	
Demographics		
Age, years [Mean (SD)]	[38.5 (19.9)]	
0 - 17	642	(17.9)
18 - 34	873	(24.2)
35 - 49	1,000	(27.8)
50 - 64	690	(19.2)
≥ 65	393	(10.9)
Female gender	1,954	(54.3)
Index year		
1997	605	(16.8)
1998	1,035	(28.8)
1999	1,168	(32.5)
2000	790	(21.9)
Number of previous antiepileptic drug trials (prior and concurrent)		
None	218	(6.1)
1	856	(23.8)
2	1,263	(35.1)
≥ 3	1,261	(34.0)
Concomitant use of other antiepileptic drug trials		
Carbamazepine	1,510	(42)
Valproate	1,424	(39.6)
Phenytoin	566	(15.7)
Vigabatrin	534	(14.8)
Concomitant use of other medication		
Antidepressants	352	(9.8)
Antipsychotics	243	(6.8)
Benzodiazepines[1]	925	(25.7)
Lithiumsalts	53	(1.5)
Migraine abortive drugs	118	(3.3)
Observation window, in years [Mean (SD)]	[4.6 (0.8)]	

[1] Others than clobazam, clonazepam, or diazepam.

discontinuation rate at three years was 32% (figure 2). Addition of another antiepileptic drug increased linearly by approximately 10% per year for the first three years after initiation of lamotrigine. Clobazam, topiramate and gabapentin were most frequently used as add–on antiepileptic drug.

Figure 2. Cumulative Hazard rates: patterns of discontinuation or add-on



Cumulative hazard rates for occurrence of add-on pattern of use ( ); discontinuation pattern of use ( ); and both patterns of use combined ( ).

In total, there was a change in therapy (either discontinuation or add–on) in approximately 52% of the study population after three years of follow–up.

Usage patterns of lamotrigine treatment stratified according to various baseline characteristics are shown in table 3. Males were as likely to continue treatment as females. Patients aged 65 years or above discontinued treatment at an earlier phase (RR 1.35; 95% CI 1.08 – 1.68). Addition of another antiepileptic drug after the start of lamotrigine treatment was less likely for patients that used valproic acid concomitantly (RR 0.51; 95% CI 0.29 – 0.90).

Prior use of migraine abortive drugs lead to a more rapid onset in discontinuation of lamotrigine (RR 1.39; 95% CI 1.03 – 1.88). Patients on antidepressants prior to the start of lamotrigine were more likely to have a change in lamotrigine therapy (RR 1.60; 95% CI 1.35 – 1.88).

Overall, patients with a history of earlier antiepileptic drug treatment were more likely to continue lamotrigine treatment compared to patients who had no background of antiepileptic drug–treatment prior to using lamotrigine (RR 0.71; 95% CI 0.58 – 0.89). Stratification by the number of filled lamotrigine prescriptions (one versus more than one prescription) showed that 7% of all patients (n = 257) discontinued lamotrigine therapy after filling just one prescription. Patients without a history of antiepileptic drugs were more prone for rapid discontinuation, 47 patients (22%) discontinued therapy after filling one prescription, compared to 6% (n = 210) in the group with a history of antiepileptic drugs.

Table 3. Determinants of lamotrigine discontinuation or failure

Covariant	Discontinuation (n = 951) RR [95%CI][1]	Add-on (n = 534) RR [95%CI][1]	Overall (n = 1485) RR [95%CI][1]
Socio-demographics			
Age			
0 - 17 year	0.92 [0.72 - 1.21]	1.26 [0.95 - 1.68]	1.03 [0.86 - 1.25]
18 - 34 year	1.00 [reference]	1.00 [reference]	1.00 [reference]
35 - 49 year	0.98 [0.81 - 1.17]	0.81 [0.64 - 1.02]	0.91 [0.79 - 1.05]
50 - 64 year	1.20 [0.99 - 1.45]	0.77 [0.60 - 1.08]	1.01 [0.86 - 1.18]
≥ 65 year	1.35 [1.08 - 1.68]	0.79 [0.56 - 1.13]	1.13 [0.94 - 1.36]
Gender			
Male	1.00 [reference]	1.00 [reference]	1.00 [reference]
Female	1.09 [0.96 - 1.24]	0.89 [0.75 - 1.05]	1.01 [0.91 - 1.12]
Index year			
1997	1.00 [reference]	1.00 [reference]	1.00 [reference]
1998	1.30 [0.98 - 1.59]	1.49 [0.36 - 6.10]	1.21 [0.89 - 1.36]
1999	1.27 [0.96 - 1.56]	1.21 [0.59 - 2.45]	1.19 [0.91 - 1.39]
2000	0.93 [0.74 - 1.17]	1.18 [0.77 - 1.81]	1.11 [0.92 - 1.33]
Previous number of antiepileptic drug trials			
None	1.00 [reference]	1.00 [reference]	1.00 [reference]
≥ 1	0.61 [0.48 - 0.78]	0.75 [0.61 - 0.94]	0.71 [0.58 - 0.89]
Concomitant antiepileptic drugs[2]			
Carbamazepine	0.85 [0.71 - 1.10]	1.07 [0.75 - 1.51]	1.06 [0.81 - 1.38]
Valproate	1.17 [0.77 - 1.78]	0.51 [0.29 - 0.90]	0.73 [0.63 - 0.84]
Phenytoin	0.77 [0.63 - 1.04]	1.08 [0.85 - 1.37]	1.02 [0.83 - 1.26]
Vigabatrin	0.81 [0.61 - 1.08]	1.15 [0.82 - 1.61]	0.95 [0.76 - 1.18]
Prior use of comedication[2]			
Antidepressants	1.85 [1.54 - 2.23]	1.23 [0.87 - 2.31]	1.60 [1.35 - 1.88]
Antipsychotics	1.12 [0.89 - 1.43]	0.79 [0.54 - 2.31]	1.03 [0.85 - 1.26]
Benzodiazepines	1.17 [1.01 - 1.34]	1.24 [0.81 - 1.42]	1.24 [0.94 - 1.40]
Lithiumsalts	0.77 [0.48 - 1.23]	0.73 [0.27 - 2.04]	0.82 [0.54 - 1.24]
Migraine abortive drugs	1.39 [1.03 - 1.88]	1.43 [0.89 - 2.31]	1.39 [1.08 - 1.79]

[1] Relative risk [RR] versus continued use, [2] Presence versus absence (reference)

Table 4. Randomised clinical trials of add-on lamotrigine in patients with refractory epilepsy

Characteristics	Matsuo et al. (1)	Messenheimer et al. (2)	Marson et al. (3)[1]	Dutch cohort
Study design and Demographics				
Design	RCT, parallel	RCT, crossover	Meta-analysis	Observational, cohort
Patient selection	chronic epilepsy	chronic epilepsy	chronic epilepsy	Population-based
Number of patients,	216	88	1,000	3,598
n (LTG:placebo)	143:73	46:42	664: 336	3,598:0
Male:Female	67:149	41:47	486:514	1644:1954
Mean age (y) (range)	33 (18 – 63)	35 (18 – 64)	n.a. (15 – 67)	39 (0 – 99)
Duration of follow-up (weeks)	24	14	8 - 24	26 - 222
Concurrent antiepileptic drug therapy, n (%)				
None	0	0	0	218 (6)
1 antiepileptic drug	86 (40)	36 (41)	n.a.	856 (24)
2 antiepileptic drugs	115 (53)	50 (57)	n.a.	1,263 (35)
3 antiepileptic drugs	15 (7)	2 (2)	n.a.	1,261 (34)
CBZ	158 (73)	67 (76)	n.a	1,510 (42)
PHT	76 (35)	40 (45)	n.a.	566 (16)
VPA	0[2]	0[2]	n.a.	1,424 (40)
Overall discontinuation rate	**13%**	**4%**	**19%**	**34%**

[1] Meta-analysis including trials by Matsuo et al, Messenheimer et al, unpublished trials and trials with less than 25 patients in the lamotrigine treatment group.

[2] Concurrent use of valproic acid was an exclusion criterion in clinical trials. N.a. = not analysed.

Comparison with reported clinical trials

Study characteristics of patients in the add–on randomised controlled trials compared with those in the present study are shown in table 4. 1,000 Patients were included in the randomised controlled trials and the length of follow–up ranged from eight weeks to six months.

Excluded from the randomised controlled trials were patients under 15 years of age, and above 67 years of age. These age categories comprised more than one fourth in our cohort of patients. Lamotrigine was used only as an add–on drug in these trials, whereas in the present study 6% of patients had no history of antiepileptic drugs. Concurrent use of valproate was not allowed in the clinical trials, in the present study 40% of patients had concurrent use of valproate. The reported estimates of the discontinuation rates at the end of the trial periods ranged from 4 to 19%. In the present study the discontinuation rate was 10% at eight weeks, 20% at 6 months and 25% at 12 months after initiation of lamotrigine.

DISCUSSION

The baseline characteristics of this Dutch population–based cohort differed from those reported from clinical trials, with respect to age, concurrent use of specific antiepileptic drugs, and length of follow–up. This may be explained by the use of lamotrigine in a broader population of epilepsy patients, including those with less severe epilepsy, and newly diagnosed epileptics starting with lamotrigine because of intolerable side effects from their previous treatment rather than because of inadequate seizure control. As a consequence, data from efficacy studies may not reflect the outcome of lamotrigine therapy in daily practice.

Retention time as an indicator for effectiveness in general practice, reflects a drug's (1) efficacy; (2) tolerability/side effects and (3) ease of use (compliance) (9–11). Addition of another antiepileptic drug may reflect insufficient seizure control with lamotrigine. The rate of use of an additional antiepileptic drug may therefore reflect lack of efficacy. Tolerability or side effects are possibly reflected by the discontinuation rate (without previous addition of another antiepileptic drug). Attrition rate appeared to be highest in the first year (25%) and slowed in subsequent years. Approximately 7% of patients on lamotrigine filled just one prescription. The relatively high discontinuation rate in the first year of therapy possibly reflects the rather difficult administration of lamotrigine at the start of therapy. The drug should be carefully titrated in order to overcome adverse events, particularly rash (12). Approximately 6% of the cohort population had not used antiepileptic drugs previously. The discontinuation rate was significantly higher in this patient group. In this group of patients 22% stopped with lamotrigine therapy after filling just one prescription. Reported predictors of non–compliance are monotherapy, and uncomplicated epilepsy (13). Another possible explanation is the availability of an increasing number of antiepileptic drugs for patients with newly diagnosed epilepsy, and physicians are possibly likely to change treatment sooner.

There are few published population–based follow–up studies of lamotrigine. Wong et al. reported on the long–term retention of add–on lamotrigine in patients with refractory epilepsy (n = 1,050) and treated in tertiary referral epilepsy clinics in the United Kingdom (UK) (14). They estimated a retention rate for lamotrigine of 48% at three years after the start of therapy, compared to approximately 68% in our study. In the UK, new antiepileptic drugs (gabapentin, lamotrigine, vigabatrin, and topiramate) were available in the UK from the early 1990s onwards. In the Netherlands, registration of lamotrigine was in 1995, between that of vigabatrin in 1990, and gabapentin and topiramate in 1999. The retention rate on lamotrigine was higher in our study possibly because other alternatives were not available for patients with ongoing refractory epilepsy. Furthermore, the UK follow up studies focussed on a group of patients with difficult–to–manage epilepsy. The reason for lamotrigine initiation in this patient group is seizure control. It is possible that our study included a broader population with

respect to disease severity and reasons for starting with lamotrigine. The retention rate of lamotrigine in patients switching from conventional antiepileptic drugs because of intolerable side effects could be better than in those who start lamotrigine for better seizure control.

Another explanation for the observed differences may be an overestimation of the retention rate in our study. The date of discontinuation was defined as the date of the last recorded lamotrigine prescription plus the duration of that prescription. Moreover, the actual time of discontinuation of lamotrigine could not be measured, but was assumed if a minimum follow–up period of 180 days exceeded the last lamotrigine prescription. This approach may have resulted in an underestimation of the proportion of patients stopping lamotrigine therapy.

Limitations of this study, include absence of clinical information in the pharmacy–based data. No individual patient information was available on factors such as duration of disease, seizure classification and seizure frequency. These factors may also be associated with continuity of therapy, e.g. generalised epilepsy is associated with higher retention rates of lamotrigine compared to partial epilepsy (14). Also, it remains uncertain whether people continuing lamotrigine in the database, experience improved seizure control, long–term. Another limitation of using prescription data is that the use of lamotrigine is not exclusive to epilepsy treatment, but extends to the treatment of bipolar disorder, migraine, or neuralgic pain (15–17). Shackleton et al. estimated the prevalence and incidence of epilepsy using the PHARMO database, which contain the medication histories of approximately 300,000 individuals (18). They validated the use of antiepileptic drugs by checking medical diagnoses of a proportion of identified antiepileptic drug users from general practitioners and hospital records. It appeared that certain antiepileptic drugs are frequently used for other indications, as only half of the patients using carbamazepine monotherapy and 5% of patients using clonazepam monotherapy had epilepsy. However, epilepsy was present in 93% of patients using more than one antiepileptic drug. As 95% of the new lamotrigine users in our population was on polytherapy, it is very likely that the large majority of these individuals had epilepsy. Data from a survey of 1,819 patients using lamotrigine, after failure of at least one antiepileptic drug, showed that off–label use was less than 6% (own data; not published).

The use of antidepressant drugs in patients with epilepsy deserves further attention because of the widespread conviction that these drugs facilitate seizures (19,20). Moreover, lifetime prevalence of depression in epilepsy is higher than in the non–epilepsy population (21). Lamotrigine is an antiglutamatergic agent with activating effects (i.e. activation, weight loss) and has been postulated as an effective drug in treating epileptic patients with depressive co–morbidity (22). In this study, however, a higher failure rate of lamotrigine was observed, indicating that the position of lamotrigine in the treatment of this subgroup of patients needs further attention. It is also possible, that lamotrigine

was used as an antidepressant or as a drug against neuropathic pain in this group of patients.

This study defines the usage patterns of lamotrigine in a large cohort of patients. While treatment retention rate was better than reported previously, there was still a substantial proportion of patients who discontinued treatment. The observed use–patterns are likely to be reflected in populations other than the Dutch. Population–based linkage of pharmacy data with other clinical data would help in better defining the effectiveness of lamotrigine.

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Recruitment of a cohort of lamotrigine users through community pharmacists: differences between patients who gave informed consent and those who did not

3.1

ABSTRACT

Objective

Community pharmacists may function as intermediaries in the recruitment of a population–based cohort of patients using specific drugs. In this study baseline characteristics and the retention rate of patients that gave informed consent, refused and did not answer were compared.

Methods

A total of 1,819 patients using the new antiepileptic drug (AED) lamotrigine were asked to provide informed consent for a retrospective chart study via their individual pharmacist. Four possible reactions resulted from the consent question: active consent, active refusal, passive refusal, and non–informed. Patient characteristics and lamotrigine retention rate of the different groups were compared.

Results

Pharmacists did not inform a total of 183 patients (10%). Of the remaining patients, a total of 968 (59%) gave consent; 101 (6%) actively refused, and 567 (35%) did not respond. Age, burden of illness, psychotropic co–medication, and continuation of lamotrigine therapy were related to active consent. Lamotrigine retention rate in patients that gave consent was higher than in other patients.

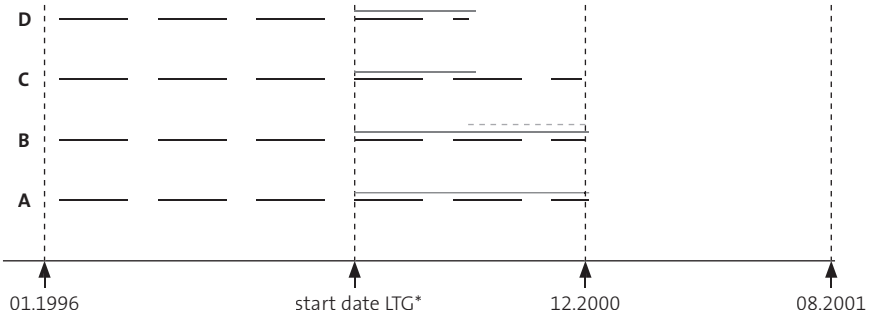
Discussion

Patient recruitment with community pharmacists as intermediaries for observational studies on the effects of (new) drugs is feasible, and allows access to a broad population of patients. The recruitment procedure, however, may lead to selection bias.

INTRODUCTION

Electronic records of dispensed prescription drugs obtained from pharmacies are a valuable source to evaluate drug effects while used in clinical practice (1,2). Strong points of pharmacy data in the Netherlands are: (1) a large catchment area (90% of the population); (2) a high patient–pharmacy allegiance; (3) the use of sophisticated and standardised pharmacy software. However, a drawback of pharmacy data in general is the absence of clinical information on indications for use and on outcomes. Person–specific data on diagnosis and course of disease can only be obtained from medical records after consent by the individual patient, as it is a basic right of the patient to be assured that all medical and personal data are confidential. It has been shown that the informed consent procedure as generally applied in randomised controlled clinical

Figure 1. Patterns of lamotrigine use



Prescription data were collected in the time frame between 1996 and 2000. The informed consent procedure started in August 2001. Information from all prescriptions (observation window, dash-line) and lamotrigine prescriptions (solid line) was used to measure lamotrigine retention and to define patterns of use. A: continuation of lamotrigine; B: add-on of another antiepileptic drug (dotted line) after the start of lamotrigine; C: discontinuation of lamotrigine (more than 180 days between end date of lamotrigine and end of observation window). Probable loss to follow-up (D) was defined if no prescription was filled after 30 June 2000.

*hypothetical starting date

trials results in a selected group of patients, that may differ with respect to relevant prognostic characteristics from the patients who refuse participation (i.e. selection bias) (3,4). Whether this phenomena also occurs in observational studies is less well studied. The goal of this study is to evaluate whether the consent procedure in an observational study into the effectiveness of the new, costly drug lamotrigine induces selection bias.

METHODS

Study setting and design

The present study is part of a larger research project addressing the effectiveness of lamotrigine in daily clinical practice. The methods of data collection and the analysis of prescription data have been described elsewhere (5). In brief, community pharmacists (n = 1428, 90% of all Dutch community pharmacies in 2001) were asked to participate in the formation of a cohort of lamotrigine users. They provided complete dispensing histories of all patients who had at least one lamotrigine prescription filled between 1 January 1996 and 31 December 2000. The collected data included patient characteristics (age, date of birth, postal code) and details (drug name, dispensing date, number of units dispensed, dosage regimen, type of prescriber) of all filled prescriptions of lamotrigine as well as all other drugs. Over 70% of the pharmacies responded to our request, resulting in a research database consisting of 6,544 patients. For a retrospective chart review

study into the effectiveness of lamotrigine, all patients were identified from this cohort who met all of the following criteria:

- date of first lamotrigine prescription (index date) after 1 August 1997;
- a minimum age of 18 at the index date;
- availability of pharmacy data for at least one year before the index date;
- prior use of at least one other antiepileptic drug before the index date.

From a total of 3,335 patients who met these inclusion criteria, 1,819 patients were randomly selected to participate in the retrospective chart study on the effectiveness of lamotrigine. A written informed consent from patients was required to acquire access to the medical charts, and we asked for this consent via a recruitment letter. The community pharmacists (n = 466) were asked to forward this recruitment letter to the patients, who were identifiable for the pharmacist through the patient identification code. In case a pharmacist decided not to forward the information to a patient, he was asked to provide the reason. Patients were asked to provide their written informed consent and the indication for lamotrigine use. Patients who refused to participate were asked to state the reason for their refusal on the informed consent sheet and return it. In total, this procedure resulted in four possible reactions to the consent question: (1) active consent; (2) active refusal, (3) passive refusal (no answer from informed patients) and (4) non–informed (pharmacist did not forward the recruitment letter).

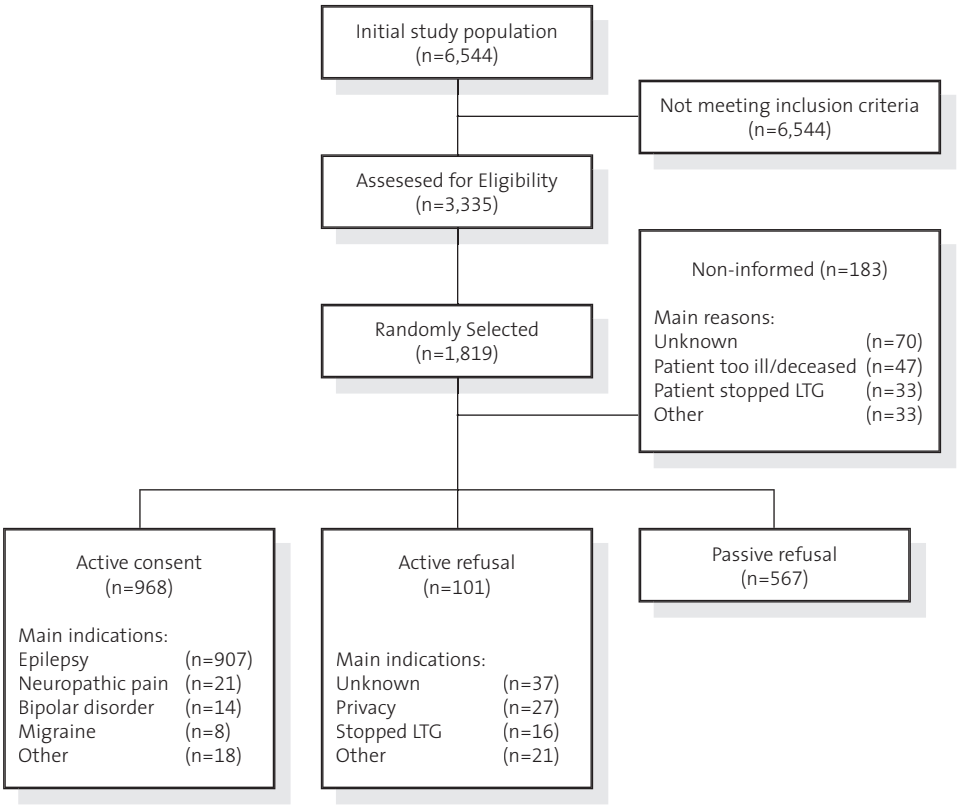
Data collection

Data on demographic and socio–economic background were available from the prescription records. The background characteristics we analysed were age, gender, urbanisation level and affluence of the neighbourhood. Neighbourhoods with over 40% inhabitants with a yearly income after taxes below € 12,000 were classified as low–income using postal code information.

Pharmacoepidemiological characteristics such as previous use of other antiepileptic drugs, concomitantly used medication and patterns of lamotrigine use were determined from prescription records. Analysis of co–medication included prescriptions of psychotropic drugs and migraine abortive drugs in the year before the index date.

Each patient was classified in one of three mutually exclusive usage patterns of lamotrigine: continuation, discontinuation or addition (figure 1). Discontinuation of lamotrigine was defined as a period of at least six months between the last refill date of lamotrigine and the end of follow–up. Add–on was defined as addition of another antiepileptic drug to lamotrigine, without discontinuation of lamotrigine therapy. In addition, loss to follow–up was assumed if a patient did not have prescriptions filled after 30 June 2000.

Figure 2. Flow diagram of recruitment procedure



In order to analyse whether burden of illness was associated with non–response, a Chronic Disease Score (CDS) was calculated based upon prescriptions filled in the last year of the observation window for each patient (6).

Data analysis

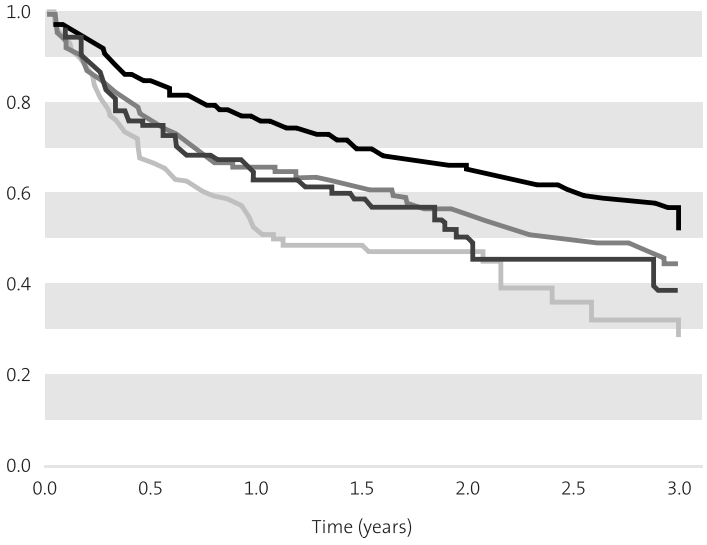
Patient characteristics were described and compared between the different response groups. Chi–square test was used to compare categorical variables. The strength of the association between various determinants and giving non–consent was assessed with Cox proportional hazard analysis and expressed as hazard ratios (HR) with 95% CI. Finally, differences in lamotrigine retention rate between the active consent group and the non–consent group were assessed with Kaplan–Meier and Cox regression analysis. The retention time was analysed from the index date to the first occurrence of one of the following events (figure 1): discontinuation of lamotrigine therapy; add–on of another antiepileptic drug; or end of study (censored).

Table 1. Comparisons of characteristics between different consent groups

Characteristics	Active consent n = 968	Active refusal n = 101	Passive refusal n = 567	Non-informed n = 183	Total population n = 1819
Sociodemographic					
Male gender	440 (45.5)	42 (41.6)	258 (45.5)	91 (49.7)	831 (45.7)
Age category:					
18 – 44 years	447 (46.2)	47 (46.5)	297 (52.4)	79 (43.2)	870 (47.8)
45 – 65 years	374 (38.6)	42 (41.6)	189 (33.3)	55 (30.1)	660 (36.3)
≥ 65 years‡	147 (15.2)	12 (11.9)	81 (14.3)	49 (26.8)	289 (15.9)
Low socio-economic status†	438 (45.2)	40 (39.6)	297 (52.4)	92 (50.3)	867 (47.7)
Urbanisation level:					
< 1000 addresses / km²	373 (38.5)	39 (38.6)	190 (33.5)	65 (35.5)	667 (36.7)
1000 – 1499 addresses / km²	238 (24.6)	32 (31.7)	119 (21.0)	43 (23.5)	432 (23.7)
≥ 1500 addresses / km²‡	357 (36.9)	30 (29.7)	258 (45.5)	75 (41.0)	720 (39.6)
Pharmacoepidemiologic					
Number of previous AEDs:					
1	251 (25.9)	33 (32.7)	161 (28.4)	56 (30.6)	501 (27.6)
2	361 (37.3)	32 (31.7)	215 (37.9)	58 (31.7)	666 (36.6)
≥3	356 (36.8)	36 (35.6)	191 (33.7)	69 (37.7)	652 (35.8)
Chronic Disease Score:					
0 - 2	565 (58.4)	55 (54.4)	339 (59.8)	84 (45.9)	1043 (57.3)
3 - 5	250 (25.8)	25 (24.8)	138 (24.3)	42 (23.0)	455 (25.0)
≥ 6‡	153 (15.8)	21 (20.8)	90 (15.9)	57 (31.1)	321 (17.7)
Concomitant use of other medication:					
Antidepressants‡	74 (7.6)	11 (10.9)	69 (12.2)	30 (16.4)	184 (10.1)
Antipsychotics‡	40 (6.0)	5 (4.9)	34 (6.0)	21 (34.4)	100 (5.5)
Lithiumsalts	8 (0.8)	1 (0.9)	7 (1.2)	5 (2.73)	21 (1.2)
Migraine abortive drugs‡	21 (2.1)	8 (7.9)	16 (2.8)	1 (0.05)	46 (2.5)
Patterns of use:					
Continuation	667 (68.9)	57 (43.6)	361 (63.7)	104 (56.8)	1189 (65.4)
Add-on†	134 (13.8)	12 (11.9)	53 (9.4)	19 (10.4)	218 (12.0)
Discontinuation‡	167 (17.3)	32 (32.0)	153 (27.0)	60 (32.8)	412 (22.6)
Loss to follow-up†	35 (3.6)	7 (6.9)	50 (8.8)	69 (37.7)	161 (8.9)
Observation window, days (mean ± SD)‡	1681 ± 288	1667 ± 336	1643 ± 315	1505 ± 376	1650 ± 313
Lamotrigine retention time, days (mean ± SD)‡	579 ± 403	467 ± 359	475 ± 392	344 ± 335	516 ± 398

Values are number of patients with percentages in parentheses unless otherwise noted. CDS, chronic disease score; SD, standard deviation. †p-value < 0.05, using Chi-square test. ‡p-value < 0.01, using Chi-square test.

Figure 3. Kaplan-Meier estimates of lamotrigine retention rate



Kaplan-Meier estimates of cumulative lamotrigine retention rate in the active consent group (●), the active refusal group (●), the passive refusal group (●) and the non-informed group (●).

RESULTS

Baseline characteristics

Between August 2001 and August 2002, 1,819 patients were asked to provide informed consent through community pharmacists. The breakdown of response is shown in figure 2. In 183 cases (10.1%) the pharmacist decided not to forward the research letter. Of the remaining 1,635 patients, 1,069 (65%) responded. Of the responders, 101 (6%) actively refused participation, the main reasons, if given, being "invasion of privacy" or "discontinuation of lamotrigine" (16%). All in all, 968 (59%) provided informed consent. Lamotrigine was predominantly used for the treatment of epilepsy in the active consent group of patients (94%).

Table 1 shows the baseline characteristics of the four different response groups and the total study population. In comparison to the active consent group, patients who were not informed through the pharmacist were older, used antidepressants or antipsychotics more often and had higher CDS scores. Loss to follow-up was more prevalent in the non-informed group compared to the active consent group. Those who did not respond (passive refusal) more often used antidepressants, lived in poor neighbourhoods and in more highly urbanised regions than those who did. Cox regression data is shown

Table 2. Determinants for not giving consent

Characteristics	Non-consent group[1] (n = 851) HR (95% CI)	Refusal group[2] (n = 668) HR (95% CI)
Sociodemographic		
Gender (male vs. female)	1.01 (0.89 – 1.17)	1.01 (0.89 – 1.21)
Age category:		
18 – 44 years	reference	reference
45 – 65 years	0.93 (0.80 – 1.09)	0.92 (0.78 – 1.09)
≥ 65 years	1.49 (1.22 – 1.81)	1.26 (0.99 – 1.60)
Income (≥ € 12,000 vs. < € 12,000)	1.10 (0.96 – 1.25)	1.10 (0.95 – 1.28)
Urbanisation level:		
< 1000 addresses / km²	reference	reference
1000 – 1499 addresses / km²	1.02 (0.85 – 1.23)	1.03 (0.84 – 1.27)
≥ 1500 addresses / km²	1.23 (1.05 – 1.43)	1.27 (1.01 – 1.51)
Pharmacoepidemiologic		
CDS (1-point increments):		
0 – 2	reference	reference
3 – 5	1.12 (0.92 – 1.36)	1.05 (0.85 – 1.31)
≥ 6	1.42 (1.20 – 1.69)	1.24 (1.01 – 1.53)
Number of previous AEDs (≥ 2 vs. 1)	1.34 (1.16 – 1.55)	1.33 (1.12 – 1.57)
Co-medication (presence vs. absence)		
antidepressants	2.16 (1.77 – 2.64)	2.01 (1.64 – 2.63)
antipsychotics	1.36 (0.96 – 1.76)	1.21 (0.88 – 1.67)
lithiumsalts	2.14 (1.24 – 3.70)	1.79 (0.89 – 3.59)
migraine abortive drugs	1.49 (1.00 – 2.23)	1.74 (1.16 – 2.61)
Patterns of use (presence vs. absence)		
Add-on	1.88 (1.58 – 2.15)	1.96 (1.64 – 2.33)
Discontinuation	3.98 (3.41 – 4.66)	4.13 (3.46 – 4.94)
Loss to follow-up	2.98 (2.50 – 3.61)	2.46 (1.87 – 3.23)

[1] Non-consent group consisted of active refusal, passive refusal and non-informed groups.

[2] Refusal group consisted of active refusal and passive refusal groups.

in table 2. Higher age (HR 1.49, 95% CI 1.22 – 1.81), highly urbanised regions (HR 1.23, 95% CI 1.05 – 1.43), CDS scores above 6 (HR 1.42, 95% CI 1.20 – 1.96) and use of two or more antiepileptic drugs are significantly related to non-consent. Further the use of antidepressants (HR 2.16, 95% CI 1.77 – 2.64), lithium (HR 2.14, 95% CI 1.24 – 3.70), and antimigraine drugs (HR 1.49, 95% CI 1.00 – 2.23) were significantly associated with non-consent. The analysis was repeated after excluding the non-informed group. It revealed the same set of significant associations, except that higher age, and use of lithium lost significance.

Retention rate analysis

Addition of another antiepileptic drug and discontinuation of lamotrigine were significantly related to non-consent (table 1 and 2). The lamotrigine discontinuation rate was significantly higher in the active refusal group (HR 1.58, 95% CI 1.15 – 2.15), the non-informed group (95% HR 2.06, CI 1.61 – 2.62) and the passive refusal group (HR 1.43, 95%CI 1.20 – 2.70) than in the group who gave active informed consent (figure 3).

DISCUSSION

In pharmacoepidemiology, it is important to link person-specific drug use data to clinical outcome data (7). The present study shows that it is feasible to use a pharmacy-based recruitment system for this goal, as it facilitates access to a broad population of patients and drug-usage patterns without violating the patient's privacy. Pharmacy-based recruitment, however, is not without selection bias. First, community pharmacists unintentionally applied selection criteria before approaching their patients. They approached fewer patients who were elderly or had other (chronic) diseases. These results are probably closely related, as elderly patients are more often chronically ill than patients in other age categories. Further, in correspondence with previous studies, consent was less often obtained among older people, among patients with a higher burden of disease, or among people living in highly urbanised neighbourhoods (8,9). Consent rates were also lower among patients that used antidepressants, lithium and migraine abortive drugs. These drugs can be considered as markers for off-label use of lamotrigine. Patients using lamotrigine for other indications are possibly less likely to give consent for a study that evaluates the effectiveness of the drug as an antiepileptic drug. Failure of lamotrigine was a reason for pharmacists to refrain from approaching patients, and also for patients to either actively deny consent or refrain from responding. Some well-known reasons for non-response like no personal benefit, no interest in the topic, or fear of intrusion of privacy were possibly more prevalent among patients who had stopped or failed lamotrigine treatment (10). As a consequence of the response bias, the retention rate of lamotrigine was significantly higher in the active consent

group compared to the non–consent group. In observational studies retention time is a crude measure of effectiveness, an outcome measure that encompasses efficacy and tolerability. One could argue that the strength of the association between determinant and outcome is not changed by the fact that some subjects are overrepresented in the sample (11). However, the goal of the study project is to estimate the effectiveness of lamotrigine on a population–based scale, and in this case accurate representation remains essential. A higher response rate would have enhanced representation, and probably have minimised the occurrence of bias. Response success depends to a great extent on the way suitable subjects are approached (11). Perhaps either the pharmacy–based approach (instead of recruitment by the treating physician) or the retrospective setting of this study resulted in a response rate that was too low to avoid bias occurrence. Sturkenboom et al. recruited women who were exposed to the drug acitretin for a retrospective cohort study in the Netherlands (12). Recruitment was done by dermatologists, pharmacists and dispensing general practitioners. Dermatologists recruited only 24% of the suitable patients, whereas the others attained 42% response. Also, the majority of women (60%) recruited by dermatologists mentioned that they were just as likely to have given consent if their pharmacist had recruited them. The response rate in the present study was similar to the one reported by Sturkenboom et al: 60% if the non–informed group was excluded.

Our conclusion is that the creation of unbiased personal histories (including both data on various exposures and outcomes) is a crucial requirement in pharmacoepidemiology (7). Pharmacy–based recruitment has the potential to reach a broad population. Selection bias, however, may lead to misrepresentation of outcome data.

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Effectiveness of lamotrigine in clinical practice: results of a retrospective population-based study

3.2

ABSTRACT

Objective

Evaluation of the effectiveness of lamotrigine in a population–based cohort of epilepsy patients.

Methods

Medical charts of 360 patients treated in 37 centres in the Netherlands were reviewed. Effectiveness of lamotrigine therapy was assessed during the first year of use, with patients serving as their own controls. Effectiveness was measured by 1) reduction in seizure frequency and 2) retention time.

Results

Effectiveness could only be assessed in 165 patients; assessment in remaining patients was not possible due to various reasons, such as insufficient medical chart information. Lamotrigine was effective in 40% of patients who had been prescribed lamotrigine because of insufficient seizure control (n=112), and 14% of these 112 patients became seizure free. Duration of epilepsy, baseline seizure frequency, valproate use, drug load and number of antiepileptic drugs used were related to effectiveness of lamotrigine. In this group, 36% continued lamotrigine throughout the first year without experiencing a >50% seizure reduction. Lamotrigine was effective in 63% of patients who received the drug because other antiepileptic drugs were not tolerated (n = 53).

Discussion

Lamotrigine is an effective drug in clinical practice. Use of retention time measures only may not correctly reflect the efficacy of antiepileptic drugs.

INTRODUCTION

During the last fifteen years six new antiepileptic drugs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate and vigabatrin) have become available for clinical practice in the Netherlands. This was a welcome development, as no new antiepileptic drugs had been introduced during the two preceding decades. In order to be licensed, these new drugs had to demonstrate efficacy as add–on drugs in patients with refractory epilepsy in placebo–controlled clinical trials. However, in daily practice these drugs are used in broader groups of patients and under less–controlled and less–monitored conditions. The effectiveness in daily practice may differ from the effectiveness found in clinical trials. Therefore the actual merit of these new drugs remains to be ascertained in daily practice (1–3).

One of these new antiepileptic drugs (AEDs), lamotrigine, has been evaluated in clinical trials in a variety of patient groups, including patients with newly–diagnosed epilepsy (4–8). In addition, the effectiveness of lamotrigine in clinical practice was evaluated in a number of observational studies, with retention time as the end point (9–13). Retention time is the period during which patients continue using the drug, and is considered to be a useful indicator of effectiveness, because it reflects seizure control as well as tolerability (14). However, retention time is only a crude indicator, as the actual changes in seizure frequency and side effects are not known. In addition, patients in these retention–time studies often were participants of previous clinical trials (9).

The aim of this study was to assess the effectiveness of lamotrigine in a population–based cohort of epilepsy patients and to assess its tolerability in this population.

METHODS

Setting and data collection

In a previous study we identified a large number of lamotrigine users through pharmacy dispensing records (15). For privacy reasons, these patients were approached through their pharmacists for permission to review their medical chart (16). Of the 968 patients who gave consent for chart review, a sample of 368 patients was selected for the actual review. This sample was representative for the group of 968 concerning hospital type, geographical area, number of antiepileptic drugs used and lamotrigine retention rate. The medical records were reviewed by a physician specialised in the field of epilepsy (C.D.). Data were collected from 32 general hospitals, 3 academic hospitals and 2 tertiary epilepsy centres. The period studied for each patient spanned from the year before the start date of lamotrigine (year –1) to the first year after start of lamotrigine (year +1). Recorded data covered the following domains:

- demographics: age, gender;
- epilepsy characteristics: epilepsy type, duration of epilepsy;
- medication: AEDs used, duration of use, dosage regimen and drug load. Drug load is the ratio between the prescribed daily dosage (PDD) and the defined daily dosage (DDD, as defined by the World Health Organisation (17)). For example, when a patient uses 600 mg of carbamazepine, this represents a drug load of 0.6, as the DDD for carbamazepine is 1000 mg. When several drugs are used, the drugs loads per drug are summed to arrive at the total drug load for that patient;
- seizure frequency in year –1 and in year +1;
- tolerability: all adverse effects registered in the medical chart for year –1 and year +1;
- reason for initiation of lamotrigine therapy.

A patient was excluded from the study if the information obtained proved that:

- there was no or an uncertain diagnosis of epilepsy, based on clinical history, seizure description and/or EEG registration;
- the patient was younger than 18 at the start date of lamotrigine (index date);
- lamotrigine was the first antiepileptic drug to be prescribed;
- the index date was before 1 August 1997, the reimbursement date of lamotrigine (i.e. as of that day, lamotrigine was reimbursed by health insurance companies) ;
- chart data for at least one year before and after the index date were not available;
- seizure frequency had been documented for less than 75% of the evaluated period;
- psychogenic pseudo-epileptic seizures were thought to be present;
- non-compliance was considered to be present.

Outcome

The primary outcome was the effectiveness of lamotrigine in daily clinical practice. Data of all eligible patients were analysed, with an intent–to–treat approach. In this mirror–image analysis, patients served as their own control group in the lamotrigine effectiveness assessment. Criteria for effectiveness during the first year of treatment depended on the reason for initiation:

1. If lamotrigine had been prescribed for inadequate seizure control with other antiepileptic drugs: lamotrigine therapy was considered effective if a reduction in mean seizure frequency of at least 50% in year +1 compared to the mean seizure frequency in year –1 was established and lamotrigine use continued for a full 12 months in year +1 without the addition of another antiepileptic drug;
2. If lamotrigine was prescribed because of adverse effects of other antiepileptic drugs: lamotrigine therapy was considered effective if there had been no clinically relevant increase in mean seizure frequency in year +1 compared to the seizure frequency in year –1 (defined as a maximum increase of less than 50%) and lamotrigine use continued for 12 months in year +1 without the addition of another antiepileptic drug.

Patients were classified as seizure free if treatment with lamotrigine led to the absence of any type of seizures for the 12 months following the start of the lamotrigine therapy.

Data analysis

Continuous variables were compared with the use of the Students' –t test, categorical variables with the Chi–square test. The relationship between patient characteristics and lamotrigine effectiveness was assessed with multiple logistic regression analysis, and expressed as odds ratios (OR) with 95% CI.

RESULTS

Patients

The medical charts and clinical notes of 360 selected outpatients were reviewed in 37 different medical centres (32 general hospitals, 3 university hospitals, 2 tertiary epilepsy centres) . This chart review led to the exclusion of more than half of these patients: 94 patients were excluded because of insufficient data on seizure frequency, 42 because charts were unavailable or because the comprised time period was too short, 27 patients had an unconfirmed diagnosis of epilepsy and 27 were excluded because lamotrigine had been initiated before the reimbursement date.

Furthermore, the chart data of three patients with progressive brain tumours and two non–compliant patients were excluded. Thus the final study population consisted of 165 patients. The study population and the population of excluded patients had similar baseline characteristics, no significant differences were found between eligible and ineligible patients in the distribution of age, gender, hospital type, duration of illness, pre–lamotrigine treatment history or lamotrigine retention time (data not shown).

The baseline demographic and clinical characteristics of the study population per hospital type are shown in table 1. In most cases (81%) lamotrigine was started after previous use of two or more other antiepileptic drugs. Significant differences were found in the distribution of patient characteristics between the three different hospital types (table 1).

Initiation of lamotrigine therapy

The baseline demographic and clinical characteristics of the study population per indication are shown in table 2. The reasons to start with lamotrigine were insufficient seizure control (68%) and antiepileptic drug intolerance (32%). In the first group, adverse effects were a concurrent problem in 13% (of the total patient group). There were significantly more women than men in the antiepileptic drug intolerance group (table 2). Also, duration of epilepsy before lamotrigine initiation was significantly shorter and mean seizure frequency significantly lower in this group than in the first. Finally, patients in the antiepileptic drug intolerance group had used less antiepileptic drugs before start of lamotrigine and their drug load was approximately half of that of the seizure control group.

Treatment effectiveness

In the total group of patients, lamotrigine was effective, according to our criteria, in 78 out of 165 patients (47%) (table 3). Effectiveness of lamotrigine therapy was significantly lower in patients that had insufficient seizure control (40%) compared to patients who were prescribed lamotrigine because of adverse effects on other antiepileptic drugs (62%). In the former group, 16 patients became seizure free.

Table 1. Demographic and clinical baseline characteristics per hospital type

Characteristics	General hospital		Academic hospital		Epilepsy centre		All hospitals	
Socio-demographic								
All Patients	93		25		47		165	
Male	37	(39.8)	13	(52.0)	22	(46.8)	72	(43.6)
Female	56	(60.2)	12	(48.0)	25	(53.2)	93	(56.4)
Age	47.7	± 15.1	42.5	± 16.7	40.1	± 12.8†	44.9	± 15.0
Epilepsy								
Epilepsy type								
Partial	85	(91.4)	21	(84.0)	41	(87.2)	147	(89.1)
Generalised	7	(7.5)	4	(16.0)	6	(12.8)	17	(10.3)
Unclassified	1	(1.1)					1	(0.6)
Duration of epilepsy (years)	14.4	±13.6	21.4	±19.3†	22.9	± 14.6†	17.9	± 15.3
Baseline monthly seizure frequency	2.1	± 4.9	4.2	± 6.4	4.9	± 6.5†	3.2	± 5.7
Pharmacoepidemiologic								
Number of previous AEDs trials								
One	29	(31.2)	1	(4.0)†	2	(4.3)†	32	(19.4)
Two	19	(20.4)	7	(28.0)†	11	(23.4)†	37	(22.4)
Three	20	(21.5)	4	(16.0)†	9	(19.1)†	33	(20.0)
Four or more	25	(26.9)	13	(52.0)†	25	(53.2)†	63	(38.2)
Concurrently used AEDs								
Carbamazepine	33	(35.5)	11	(44.0)	30	(63.8)†	74	(44.8)
Phenobarbital	5	(5.4)	0	(0)	5	(10.6)	10	(6.1)
Phenytoin	13	(14.0)	6	(24.0)	5	(10.6)	24	(14.5)
Sodium valproate	41	(44.1)	8	(32.0)†	26	(55.3)†	75	(45.5)
Vigabatrin	18	(19.4)	11	(44.0)†	7	(14.9)	36	(21.8)
Drug load	1.1	± 0.9	1.6	± 1.0	1.8	± 1.1‡	1.4	± 1.0
Reasons for starting LTG								
Lack of efficacy	43	(46.2)	10	(40.0)	37	(78.7)‡	90	(54.5)
Adverse events	40	(43.0)	8	(32.0)	5	(10.6)‡	53	(32.1)
Both	10	(10.8)	7	(28.0)	5	(10.6)‡	22	(13.3)

Values are numbers of patients with percentages in parentheses, or mean values with standard deviations (with a ± symbol)

† Statistically significant ($p \leq 0.05$) differences compared to patients from general hospitals

‡ Statistically significant ($p \leq 0.05$) differences for patients from tertiary centres when compared to patients from other hospital types.

Table 2. Demographic and clinical baseline characteristics per indication group

Characteristics	Seizure control		AED intolerance	
Socio-demographic				
All Patients	112		53	
Male	53	(47.3)	19	(35.8)
Female†	59	(52.7)	34	(64.2)
Age	44.3	± 14.9	45.5	± 15.3
Epilepsy				
Epilepsy type				
Partial	100	(89.3)	47	(88.7)
Generalised	12	(10.7)	5	(9.4)
Unclassified			1	(1.9)
Duration of epilepsy (year)†	20.4	± 15.9	12.6	± 12.4
Baseline monthly seizure frequency†	4.4	± 6.4	0.5	± 1.4
Pharmacoepidemiologic				
Number of previous AEDs†				
One	19	(17.0)	13	(24.5)
Two	21	(18.8)	16	(30.2)
Three	23	(20.5)	10	(18.9)
Four or more	49	(43.8)	14	(26.4)
Concurrent AEDs				
Carbamazepine†	58	(51.8)	16	(30.2)
Phenobarbital	9	(8.1)	1	(1.9)
Phenytoin	17	(15.2)	7	(13.2)
Sodium valproate	56	(50.0)	19	(35.8)
Vigabatrin	23	(20.5)	13	(24.5)
Drug load†	1.7	± 1.1	0.8	± 0.8

Values are numbers of patients with percentages in parentheses, or mean values with standard deviations (with a ± symbol).

† Statistically significant differences ($p \leq 0.05$) between the two indication groups.

In this group, 40 patients continued lamotrigine without experiencing a ≥ 50% seizure reduction. In the latter group, the previously non-tolerated drug was sometimes continued at a lower dose and sometimes withdrawn concurrently to the introduction of lamotrigine. Conversion to lamotrigine monotherapy was significantly lower in the seizure-control group: 8% and 37.7% respectively. The spectrum of adverse effects mentioned in the medical charts differed in the years before and after start of lamotrigine (table 4).

Table 3. Clinical outcome of lamotrigine therapy in the study population

	Seizure control (n = 112)		AED intolerance (n = 53)	
LTG treatment outcome				
Ineffective†	67	(59.8)	20	(37.8)
Effective†	45	(40.2)	33	(62.2)
Seizure free	16	(14.3)	n.a.	
Reasons for failure of LTG				
Inadequate seizure control†	50	(83.6)	7	(35.0)
Adverse events†	17	(16.4)	13	(65.0)
Discontinuation in first year	27	(24.1)	11	(20.7)
Due to rash	10	(8.9)	2	(3.8)
Retention time of LTG (days)	313	± 106	312	± 113
Conversion to LTG monotherapy†	9	(8.0)	20	(37.7)
LTG dosage (mg/day)	206	± 128	194	± 128
Range (mg/day)	12.5 – 600		12.5 – 500	

Values are numbers of patients with percentages in parentheses, or mean values with standard deviations (with a ± symbol)
n.a: not analysed
† Statistically significant differences ($p \leq 0.05$) between the two indication groups.

Table 4. Most frequently reported side effects

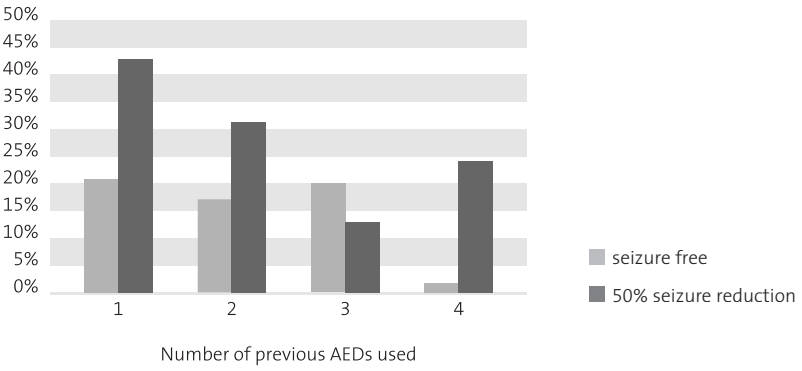
Adverse events	Year – 1 (%)	Year + 1 (%)
concentration loss	15.2	7.9
weight gain	14.8	2.4
mood disorder	9.7	11.5
diplopia/blurred vision	9.7	10.3
sleepiness	9.1	4.8
dizziness	9.1	13.3
tiredness	7.9	not mentioned
tremor	7.9	7.3
gastrointestinal complaints	6.1	9.7
hair loss	5.5	1.2
skin disorders (acne; rash)	3.6	14.5
headache	3.0	9.1

Table 5. Factors associated with success of lamotrigine therapy

Characteristics	Seizure control group OR (95% CI)		AED intolerance group OR (95% CI)	
Socio-demographic				
Gender				
Male	1.00	(reference)	1.00	(reference)
Female	1.41	(0.66 - 3.02)	2.67	(0.83 - 8.54)
Age category				
18 – 44 years	1.00	(reference)	1.00	(reference)
45 – 65 years	2.44	(0.98 - 5.58)	1.10	(0.32 - 3.78)
≥ 65 years	1.69	(0.51 - 5.61)	1.89	(0.38 - 9.39)
Epilepsy				
Epilepsy type				
Partial	1.00	(reference)	1.00	(reference)
Generalised	0.72	(0.20 - 2.55)	0.38	(0.06 - 2.49)
Unclassified	n.a.		n.a.	
Duration of epilepsy	0.96	(0.94 - 0.99)	0.98	(0.94 - 1.02)
Baseline seizure frequency	0.91	(0.84 - 0.97)	0.21	(0.12 - 5.37)
Pharmacoepidemiologic				
Number of previous AEDs trials				
One	1.00	(reference)	1.00	(reference)
Two	0.18	(0.05 - 0.70)	0.39	(0.08 - 1.96)
Three	0.33	(0.09 - 0.89)	0.30	(0.05 - 1.80)
Four or more	0.13	(0.04 - 0.43)	0.54	(0.10 - 2.93)
Concurrent antiepileptic drugs				
Carbamazepine	0.82	(0.39 - 1.76)	0.70	(0.21 - 2.30)
Phenobarbital	0.41	(0.11 - 1.47)	n.a.	
Phenytoin	0.20	(0.05 - 0.81)	n.a.	
Sodium valproate	1.24	(1.09 - 1.54)	0.53	(0.17 – 1.68)
Vigabatrin	0.59	(0.22 - 1.57)	0.96	(0.27 – 3.48)
Drug load				
0 - 1	1.00	(reference)	1.00	(reference)
1 - 2	0.45 (0.23 – 0.92)		0.35	(0.08 - 1.43)
≥ 2	0.29	(0.10 – 0.83)	n.a.	

AEDs: antiepileptic drugs.

Figure 1. Efficacy of lamotrigine related to the number of AEDs previously used



Logistic regression analysis

Logistic regression analysis showed that several characteristics were significantly associated with effectiveness in the seizure control group (table 5). Both length of duration of epilepsy (OR 0.96, 95% CI: 0.94 – 0.99) and baseline seizure frequency (OR 0.91, 95% CI: 0.84 – 0.97) were inversely related to lamotrigine effectiveness. Baseline drug load was also related to successful lamotrigine response; compared to drug loads between 0 and 1, higher drug loads were related to failure of therapy ($drugload_{1-2}$: OR 0.45, 95% CI: 0.23 – 0.92; $drugload_{\geq 2}$: OR 0.29, 95% CI: 0.10 – 0.83). The number of antiepileptic drugs used before the start of lamotrigine was significantly correlated to the successful outcome of lamotrigine therapy; the success rate (i.e percentage of patients with ≥ 50% seizure reduction) in patients that used one antiepileptic drug previously being at least threefold higher than in patients who used two or more antiepileptic drugs previously. Effectiveness of lamotrigine therapy was more likely in patients who had used sodium valproate concurrently (OR 1.24, 95% CI: 1.09–1.54). Effectiveness of lamotrigine was less likely in patients using phenytoin (OR 0.20, 95% CI: 0.05 – 0.81). There was no association in this group between treatment outcome and gender, age, epilepsy type, or use of carbamazepine, phenobabital or vigabatrin.

The impact of the number of previously used antiepileptic drugs on the effectiveness of lamotrigine in this group is illustrated in figure 1. Effectiveness of lamotrigine after failure of one antiepileptic drug was 74%, including 21% seizure–free patients. The effectiveness of lamotrigine after four previously used antiepileptic drugs was 26%, and a total of 2% became seizure free. There were no differences in effectiveness between patients with localization–related epilepsy and patients with generalised epilepsy.

In the antiepileptic drug intolerance group no individual characteristics were found to be significantly related to the treatment outcome.

DISCUSSION

This study aimed at assessing the effectiveness of lamotrigine in clinical practice. The results add to the present knowledge concerning the efficacy and tolerability of lamotrigine.

(1) Seizure control (efficacy): A higher success rate of lamotrigine therapy was found in this study than in previous add–on trials. In the first year of treatment, lamotrigine therapy was effective in 40% of the patients with refractory epilepsy. In the initial regulatory trials, with a maximum follow–up of 24 weeks, the percentage of patients experiencing a ≥ 50% reduction was lower (4;18). This difference in efficacy may be due to a broader study population in our sample, i.e. more patients who had tried only one or two antiepileptic drugs prior to lamotrigine. Seizure reduction of 50% or more is broadly accepted as the recognisable threshold of effect in add–on trials, and there is evidence that reducing a patient's seizure frequency is the most important contributor to a change in quality of life (19). However, the relevance of reducing seizures by 50% may not be obvious to individual patients. Seizure freedom is a much more relevant and easier to interpret efficacy parameter. In the seizure–control group of this study, seizure freedom was attained in 14% after addition of lamotrigine. In patients that had previously used four or more other antiepileptic drugs, addition of lamotrigine only rendered 2% seizure free, which is comparable to the 5% seizure–free rates reported in regulatory trials. However, 15 to 20% of patients who had previously used one, two or three other antiepileptic drugs, became seizure free in this group (figure 1). These data on the efficacy of lamotrigine compare favourably with the observational data reported by Kwan and Brodie (20). These authors reported seizure freedom with any drug or combination of drugs in only 4% when patients did not become seizure free on their first or second antiepileptic drug.

Our study confirms the general finding that an early response to drug therapy or a low seizure frequency confirms a favourable prognosis (21). The combination of lamotrigine and valproate seems to exhibit a favourable pharmacodynamic interaction in patients with refractory epilepsy, an observation that has been made previously (22;23).

(2): antiepileptic drug intolerance (tolerability): lamotrigine therapy was effective in 60% of the patients who started taking the drug because of adverse events with other antiepileptic drugs. In previous observational studies on the effectiveness of lamotrigine, only patients with inadequate seizure control were evaluated (9;24–26). In clinical practice, physicians also prescribe lamotrigine because the drug is known to have a more favourable side–effect profile than conventional antiepileptic drugs (6;27;28). Due to lamotrigine's mild side–effect profile, the drug is an effective alternative for cases of antiepileptic drug intolerance. In the present study, adverse effects necessitated withdrawal of lamotrigine therapy in 22% of the patients, with rash as the most common cause for discontinuation (7%). This is actually higher than in the clinical

trials; pooled trial data showed a discontinuation rate of lamotrigine therapy of 10%, rash being reported the most frequently (3.8%) as the reason for discontinuation (29). Seven of the 53 patients prescribed lamotrigine because of adverse effects on previous drug or combination of drugs, experienced a significant worsening of seizure control. However, 33 of the patients in this group responded well to lamotrigine, which implies that lamotrigine was able to maintain seizure control in these patients.

The methods of patient recruitment and reviewing charts in different medical centres employed for this study are quite laborious, certainly compared with the aforementioned retention–time studies. They do, however, have important advantages. First, our methods produce more information than retrospective studies that focus only on retention time, as the actual seizure–frequency reduction per patient and the percentage of seizure–free patients are determined. We found that 36% stayed on lamotrigine for longer than 12 months, despite their not experiencing a >50% seizure reduction. In the observational studies focusing only on retention time, more patients discontinued lamotrigine than in our study, but the study period in these studies was longer. Second, the employed methods result in studying a cross–section of patients visiting different hospital types. The retention–time studies mostly concerned patients from tertiary referral epilepsy clinics, which represent less than one third of the epilepsy population as a whole (3). As table 2 shows, patients attending tertiary clinics have a high number of previous antiepileptic drug trials, are on high drug loads and have higher seizure frequencies. These are factors that have a negative impact on the success of antiepileptic drug treatment.

The results of the present study must also be considered within the context of several limitations. First, this study only included patients who had given consent to their community pharmacist. This may have led to biased enrolment towards patients in which lamotrigine was effective (16). Second, this was a retrospective cohort study. The resultant data acquisition was non–blinded and drug selection was non–random. Third, we used a mirror–image design (patients serving as their own control group) instead of an independent control group. Physicians start lamotrigine at the peak of disease activity: either an unacceptable seizure frequency or intolerable side effects. The course of epilepsy is variable, and improvements could have occurred without any special intervention (i.e. regression to the mean). One may nevertheless claim that monitoring 12 months before and after the start of lamotrigine is sufficiently long to rule out regression to the mean as sole reason for lamotrigine effectiveness. Fourth, the data for this study were collected with the use of medical chart notes. These notes are primarly kept to aid in the treatment of individual patients, and not for outcome research. Therefore seizure counts are not always recorded into the notes, and in these cases retrospective baselines could not be obtained, and these patients had to be excluded. Nevertheless, eligible and ineligible patients seemed comparable with respect to baseline characteristics.

Despite these limitations, this study allowed us to assess the effectiveness of lamotrigine in a population–based setting. The data for the present study came from diverse regions of the country and from diverse medical centres. As such, the results are likely to be representative. Therefore, the study should be considered as complementary to the initial randomised add–on trials and subsequent post–marketing studies addressing the efficacy of lamotrigine in selected patients. It can be concluded from the present study that lamotrigine is an effective treatment option and a useful alternative for patients with varying needs, including those with inadequate seizure control and intolerable side effects.

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Cost-effectiveness of add-on lamotrigine therapy in a population-based cohort

3.3

ABSTRACT

Objective

This observational study addresses the cost effectiveness of add–on therapy with lamotrigine in a population–based cohort of patients.

Methods

Two years' observational data of 165 patients were used. The effectiveness of lamotrigine therapy during the first year was assessed, with patients as their own control group. Therapy effectiveness was measured by 1) reduction in seizure frequency and 2) retention time. A mirror design was used to compare differences in costs and effectiveness in the years before and after the start of lamotrigine therapy. The incremental cost–effectiveness ratio expressed the direct medical cost per patient treated effectively with lamotrigine.

Results

The cost of medication was € 492 (95% CI € 399 – € 583) higher after the start of lamotrigine therapy. The extra cost of lamotrigine therapy (€ 622) was partly offset by a reduction of the cost of co–medication (–€ 130, 95% CI – € 210 : – € 50). Overall, the total medical cost was € 453 higher in the first year of lamotrigine therapy than in the year before the start of lamotrigine. Lamotrigine was effective in 47% of all the patients, making the resultant incremental cost per successfully treated patient € 954 per year.

Discussion

Add–on therapy of lamotrigine for patients with uncontrolled epilepsy offers improved health outcomes. Lamotrigine therapy is associated with increased cost (€ 453) and an annual incremental cost per successfully treated patient of € 954. Both the quality–adjusted life–years data published in medical literature and the data resulting from this study provide evidence that lamotrigine could be adopted as an efficient therapy for patients with refractory epilepsy.

INTRODUCTION

Conventional antiepileptic drugs (AEDs) have traditionally been the cornerstone of clinical epilepsy management. Approximately 30% of the epilepsy patients respond poorly to these agents, either because of a lack of efficacy or because of intolerable side effects. New antiepileptic drugs have broadened the treatment options for patients with uncontrolled epilepsy, but they have higher acquisition costs than the conventional antiepileptic drugs. Because of the tension between budget constraints and the growing

treatment possibilities, health–economic evaluations are increasingly important in the field of epilepsy. These health–economic evaluations are particularly important for the treatment options of patients with refractory epilepsy, as they suffer more than other patients from the economic and social effects of their illness (1). Jacoby et al. found that the costs of illness for patients with refractory epilepsy were up to eight times the costs for those with controlled epilepsy (2). In addition, Van Hout et al. found that higher seizure frequencies are associated with increases in the cost of illness as well as with the reduced quality of life (3). Estimates of direct medical costs of patients with refractory epilepsy found in medical literature vary from € 850 to € 4,250 per year (3–7).

In order to establish a high external validity of a study, observational studies can be used to asses the effectiveness and cost–effectiveness (or efficiency), as a supplement to the establishment of the efficacy of healthcare technology in a highly controlled situation for selected patients (8). This study addresses the health economic aspects of add–on therapy with lamotrigine (LTG) in a population–based cohort of patients. The aim of this retrospective, observational cost–effectiveness analysis is: 1) to compare healthcare utilisation and cost in the year before the start of lamotrigine treatment with the year after; and 2) to relate the difference in cost to the difference in effectiveness.

METHODS

Setting

The present study took the form of a retrospective cohort study using a mirror–image design. The cost–effectiveness analysis was performed along with a detailed observational study on the effectiveness of lamotrigine. The results of the effectiveness study are published elsewhere (8). In brief, the study population consisted of 165 adult patients (≥ 18 years) who received add–on lamotrigine therapy because of uncontrolled epilepsy on conventional antiepileptic drugs or vigabatrin. All patients met at least one of the following inclusion criteria:

1. Treatment resistance, defined as a suboptimal response to a therapeutic dosage of at least one antiepileptic drug;
2. Drug intolerance, defined as intolerable side effects leading to the discontinuation of antiepileptic medication.

Data were collected from 31 general hospitals, 4 academic hospitals and 2 tertiary epilepsy centres. Data of patients who switched to lamotrigine were collected retrospectively from their medical records; data on patient characteristics, treatment outcome and healthcare utilisation were recorded. In a mirror–image design, data were extracted for one year before (year –1) and one year after (year +1) the day of switching; the sum of both mirror periods is defined as the study period.

Resource utilisation

Chart review of all epilepsy related resource utilisation was performed, with a pre–tested standard list of resource items. Resource use during the study period was directly recorded in a specially designed database. The epilepsy–related resource utilisation included hospital services, diagnostic procedures and antiepileptic medication, as specified in table 1. Type and dosage of the medication used, as well as date and reason for therapy changes, were recorded. Resources related to patient and family domain (e.g. transportation, paid care) or to other domains (e.g. time loss from work/usual activity) could not be distilled from the medical charts.

Cost valuation

Epilepsy–related direct medical cost was estimated from a healthcare perspective. In the analysis, the cost was calculated by multiplying the epilepsy related resource use of each patient with unit cost. The assignment of unit cost to the various elements of epilepsy care is based on guideline prices for economic evaluation in Dutch health care (9;10). For these unit costs, no distinction was made between the actual hospital settings (general or academic hospital, tertiary epilepsy centre). When no guideline price for an item was available, tariffs were used as shadow prices. In our study this applied to drug cost, laboratory tests and imaging procedures (table 1). All prices were expressed in euros (€ ; exchange rate in March 2005: € 1 = USD 1.3) and updated to January 2004 according to the rate of inflation by the Consumer Price Index (Statistics Netherlands, http://www.cbs.nl). Non–parametric bootstrap analysis was used to analyse differences in cost between year –1 and year +1.

Effectiveness

Lamotrigine treatment was considered to be effective if the drug was not discontinued during the first year of treatment and the following criteria were met:

1. For the Treatment resistance group: lamotrigine therapy was considered effective if a reduction in mean seizure frequency was established of at least 50% in year +1 compared with the mean seizure frequency in year –1, and no other antiepileptic drug had been added.
2. For the Drug intolerance group: lamotrigine therapy was considered effective if the therapy was tolerated and there was no clinical relevant increase in mean seizure frequency in year +1 compared with the seizure frequency in year –1 (defined as a maximum increase of less than 50%).

This outcome encompasses the efficacy endpoint used in randomised clinical trials of antiepileptic drugs (seizure reduction of at least 50%) and the effectiveness endpoint used in observational studies (retention time). The Students' t–test was used to analyse differences in effectiveness.

Table 1. Unit cost in 2004

Cost item	Cost measure	Unit cost (€)	Source of unit cost
Hospital services			
Outpatient			
Outpatient consult	per visit	62.1	guideline price
Telephonic consult	per call	31.1	guideline price
Inpatient			
Hospital visit	per admission day	316.1	guideline price
Intensive care visit	per admission day	1294	guideline price
Diagnostic procedures			
Imaging procedures			
CT scan	per procedure	160.3	CVZ tariff
EEG	per procedure	87.7	CVZ tariff
EEG, 24 hour	per procedure	740.7	CVZ tariff
MRI scan	per procedure	211.9	CVZ tariff
Laboratory procedures			
Clinical chemistry	per procedure	5.5 - 15.2	CVZ tariff
Drug monitoring	per procedure	12.8 - 21.5	CVZ tariff
Medication[1]			
Carbamazepine, 1,000 mg	per month	10.20	CVZ tariff
Phenytoin, 300 mg	per month	2.3	CVZ tariff
Vigabatrin, 2,000 mg	per month	80.2	CVZ tariff
Valproate, 1,500 mg	per month	17.2	CVZ tariff
Lamotrigine, 300 mg	per month	110.6	CVZ tariff

[1] Monthly total cost for daily defined dose based on most frequently used oral-dosage form (only the most frequently used antiepileptic drugs in this study are listed). CVZ: Dutch Health Care Insurance Board.

Cost-effectiveness analysis

The pre-specified incremental cost-effectiveness ratio (ICER) was the annual direct medical cost per patient effectively treated with lamotrigine. The ICER is calculated as:

$$\frac{[(\text{mean annual cost per patient})_{\text{year}+1} - (\text{mean annual cost per patient})_{\text{year}-1}]}{(\%\ \text{effectively treated patients})_{\text{year}+1}}$$

All health outcomes and resource utilisation were recorded for the two-year period and analysed by intention-to-treat. Normal distribution assumptions are not valid when dealing with healthcare costs, which have a right skewed distribution (11). Non-parametric bootstrap analysis was used to estimate the uncertainty of the ICER by defining the 2.5th and 97.5th percentiles of 1,000 bootstrapped replications (12). The uncertainty surrounding the ICER is presented graphically by plotting the bootstrap

Table 2. Demographic and clinical baseline characteristics per indication group

Characteristics	Seizure control		AED intolerance		Total	
All Patients	112		53		165	
Male	53	(47.3)	19	(35.8)	72	(43.6)
Female†	59	(52.7)	34	(64.2)	93	(56.4)
Age (year)*	44.3	(14.9)	45.5	(15.3)	44.9	(15.0)
Hospital type†						
General hospital	53	(57.0)	40	(43.0)	93	(56.4)
Academic hospital	17	(68.0)	8	(32.0)	25	(15.1)
Tertiary epilepsy centre	42	(89.4)	5	(10.6)	47	(28.5)
Epilepsy characteristics						
Epilepsy type						
Partial	100	(89.3)	47	(88.7)	147	(89.1)
Generalised	12	(10.7)	5	(9.4)	17	(10.3)
Unclassified			1	(1.9)	1	(0.6)
Duration of epilepsy (year)*†	20.4	(15.9)	12.6	(12.4)	17.9	(15.3)
Baseline monthly seizure frequency*†	4.4	(6.4)	0.5	(1.4)	3.2	(5.7)
Number of previous AEDs†						
One	19	(17.0)	13	(24.5)	32	(19.4)
Two	21	(18.8)	16	(30.2)	37	(22.4)
Three	23	(20.5)	10	(18.9)	33	(20.0)
Four or more	49	(43.8)	14	(26.4)	63	(38.2)
Concurrent AEDs						
Carbamazepine†	58	(51.8)	16	(30.2)	74	(44.8)
Phenytoin	17	(15.2)	7	(13.2)	24	(14.5)
Sodium valproate	56	(50.0)	19	(35.8)	75	(45.5)
Vigabatrin	23	(20.5)	13	(24.5)	36	(21.8)
Health Outcome†						
LTG therapy effective	45	(40.2)	33	(62.3)	78	(47.3)
LTG therapy not effective	67	(59.8)	20	(37.7)	87	(52.7)

Values are number of patients with percentages in parentheses, except '*': Mean (SD).
† Statistically significant differences ($p \leq 0.05$) between the two indication groups.

ICERs on a cost–effectiveness plane (13). Because the value of the highest acceptable incremental cost–effectiveness ratio is unknown, the likelihood that lamotrigine is cost–effective at different values of this threshold is plotted as an acceptability curve.

Table 3. The mean healthcare cost per patient and year in 2004

	Year before LTG	Year with LTG	Difference	95% CI
Hospital services				
Outpatient	247.6	256.5	8.9	– 12.5 : 30.2
Outpatient consult	233.5	235.8	2.4	– 17.1 : 21.9
Telephonic consult	14.2	20.7	6.50	0.4 : 12.6
Inpatient	481.6	449.7	– 31.9	– 445.0 : 381.2
Hospital stay	358.8	449.7	90.9	– 284.7 : 466.6
Intensive care stay	122.8	0	– 122.9	– 297.9 : 52.2
Subtotal	**729.3**	**706.2**	**– 23.1**	**– 438.7 : 392.6**
Diagnostic procedures				
Imaging procedures	97.6	80.3	– 17.3	– 71.7 : 37.0
CT scan	20.3	8.1	– 12.2	– 20.0 : – 4.4
EEG	53.2	65.6	12.3	– 39.4 : 64.0
MRI scan	24.1	6.7	– 17.4	– 26.6 : – 8.3
laboratory procedures	42.5	44.0	1.5	– 7.1 : 10.2
Clinical chemistry	25.1	25.8	0.7	– 5.2 : 6.6
Drug monitoring	17.4	18.2	0.8	–3.3 : 5.0
Subtotal	**140.1**	**124.3**	**– 15.8**	**– 71.0 : 39.4**
Medication				
AED co-medication	396.9	266.8	– 130.1	– 210.2 : – 49.9
Lamotrigine	0	621.7	621.7	573.0 : 670.3
Subtotal	**396.9**	**888.5**	**491.6**	**399.9 : 583.3**
Total	**1,266.3**	**1,719.0**	**452.8**	**20.9 : 884.6**

RESULTS

Demographics

The study population of 165 patients included 93 women. The mean age at the start of lamotrigine therapy was 45 years (table 2). The mean duration of epilepsy before the start of lamotrigine was 18 years. In most cases (81%) lamotrigine was started after previous use of two or more other antiepileptic drugs. Treatment resistance was the main reason (68%) to start with lamotrigine, while in the other 32% antiepileptic drug intolerance was given as reason.

Effectiveness

Lamotrigine was effective, according to our criteria, in 78 of 165 patients (47%) (table 2). Effectiveness of lamotrigine therapy was significantly lower in the treatment

Figure 1. Impact of treatment outcome on cost

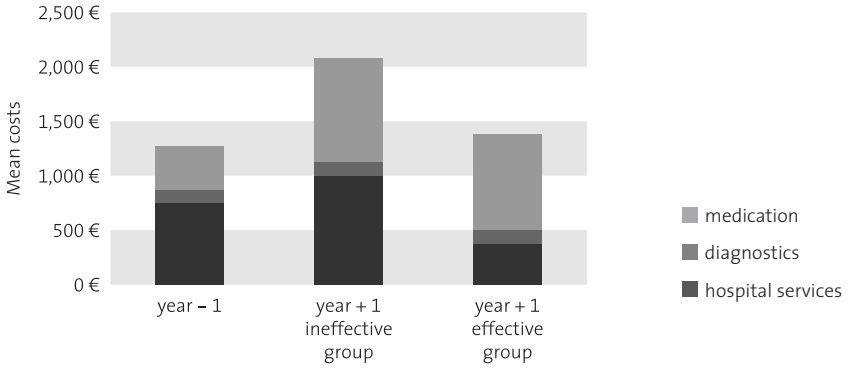
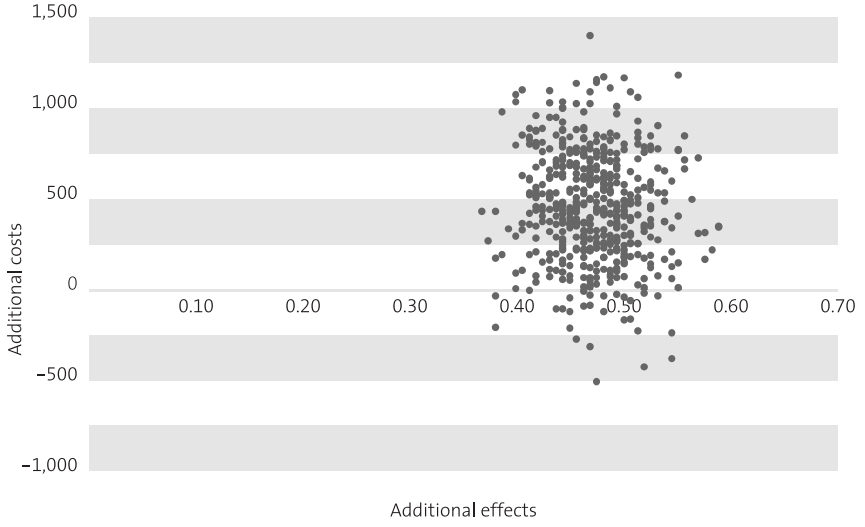
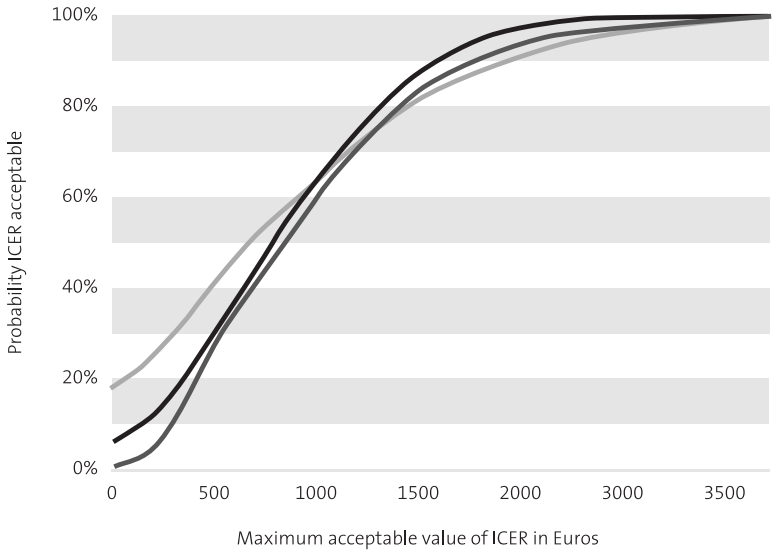


Figure 2. Bootstrap replicates of incremental cost-effectiveness ratio



1,000 Bootstrap replicates of ICER showing the joint distribution of costs and health outcomes in the cost-effectiveness plane. On the x-axis the difference in effectiveness between year+1 and year-1, on the y-axis the difference in average annual costs.

Figure 3. Cost-effectiveness acceptability curve for treatment with lamotrigine



Acceptability curves for the treatment resistance cohort ( ), drug intolerance cohort ( ) and total cohort ( ).

resistance group than in the antiepileptic drug intolerance group: 40.2% and 62.3% respectively ($p < 0.05$).

Cost

Total cost was € 1,266 in year –1 and € 1,719 in year +1, a difference of € 453 (95% CI € 21 – € 885; table 3). The cost of hospital services or diagnostic procedures was only slightly different between year +1 and year –1: – € 23 and – € 16 respectively. The costs of medication was higher in year +1 than in year –1, the difference being € 492 (95% CI € 399 – € 583).The extra cost of lamotrigine therapy (€ 622) was partly offset by a reduction of the cost of co–medication in year +1 (– € 130, 95% CI – € 210 – –€ 50). The costs in year +1 for patients treated effectively with lamotrigine were not different than in year –1 (cost difference € 84; 95% CI – € 215 – € 383; figure 1). Despite the relatively small number of patients, a cost difference compared to year –1 was seen in patients with a lack of effectiveness from lamotrigine (cost difference € 803, 95% CI € 278 – € 1,329). This was related to the relatively high cost of hospital services (mean cost € 1,017) and medication (€ 926) for these patients in year +1, as shown in figure 1.

Cost-effectiveness analysis

By definition, the effectiveness in the year –1 period was zero. The ICER per patient between year +1 and year –1 was therefore (€ 1.719 – € 1.266.3)/ (0.47–0) = € 954.

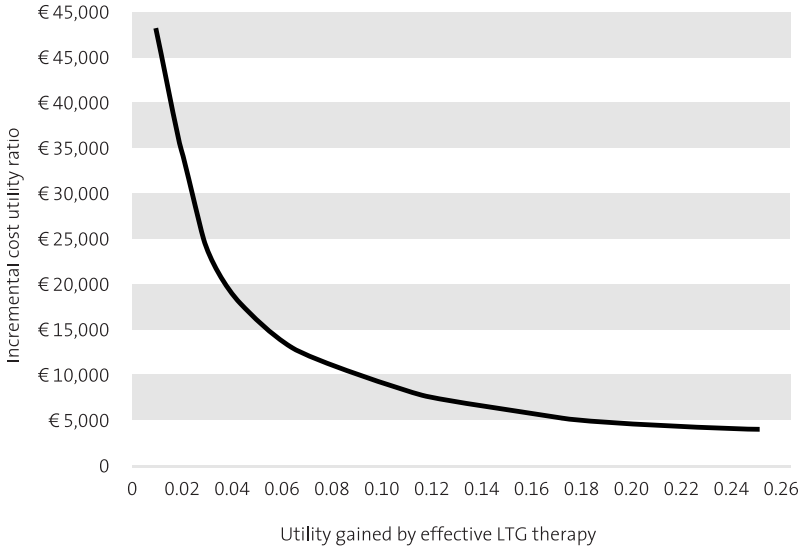
Consequently, an extra € 453 per patient was needed to increase the effectiveness of epilepsy treatment by 47%, amounting to an investment of € 954 per successfully treated patient. In figure 2, the distribution of bootstrap replicates is displayed graphically in a cost–effectiveness plane. Overall, 6% of the bootstrap replicates were found in the South–East quadrant, which indicates that lamotrigine therapy is dominant (more effective and lower costs) and 94% of replicates were found in the North–East quadrant, indicating that lamotrigine therapy is more effective, but at a higher cost. The ICER for the treatment resistance cohort was € 849, and € 1,094 for the drug intolerance cohort. The acceptability curves are shown in figure 3.

DISCUSSION

In this study the cost of lamotrigine therapy is related to the effectiveness of this intervention using data from a population–based cohort of patients from various treatment centres in the Netherlands. In the first year of lamotrigine treatment an overall effectiveness rate of 47% was found. lamotrigine treatment was associated with an average higher annual epilepsy–related cost of € 435. The largest cost difference was found in the cost of drug, as the extra cost for lamotrigine (€ 622) was only partly offset by a reduction in cost for other antiepileptic drugs (– € 130; 21% reduction). It has been argued that despite the high acquisition cost, lamotrigine may constitute an important money saver because of its fewer side effects and increased tolerability (14;15). We could not confirm overall savings for the entire cohort. For patients who had been treated effectively with lamotrigine there was no cost difference between year +1 and year –1, as savings in hospital services (€ 350) offset most of the rise in drug cost (€ 452). For patients with whom lamotrigine was not effective, cost savings were absent in year +1 and a cost increase compared with year –1 was noticed.

The direct medical cost found in this study fell within the previously mentioned range of € 850 to € 4,250 per year for patients with uncontrolled epilepsy (3–7). This study shows that the ICER associated with the add–on use of lamotrigine was € 954 per year. The economic question, based on the cost–effectiveness analysis, is whether € 954 annually for an extra patient treated effectively is good value for money. Previous studies regarding the cost–effectiveness of add–on lamotrigine do not provide relevant information, as they varied in terms of cost measures addressed, time periods covered, treatment pathways and outcome measures (16–20). These studies were based on decision–analysis models. Their validity was questioned, as their input depends on the extrapolation of trial data and estimations of expert panels (20). To address the economic question raised above, a cost–utility analysis rather than a cost–effectiveness analysis is required. Cost–utility analysis and cost–effectiveness analysis are identical on the cost side, but differ on the outcome side. In cost–utility analysis, the incremental cost

Figure 4. Relation between cost per QALY and utility value associated with lamotrigine



of a programme is compared to the incremental health improvement attributable to the programme, in which health improvement is measured in quality-adjusted life years (QALYs) gained (21). The advantage of a cost-utility analysis is that its results are more universal than a specific cost-effectiveness analysis. The results can be compared with other studies regarding different health care topics. Moreover, quantitative thresholds for cost per QALY gained have been proposed upon review of economic evaluations (21;22). If cost per QALY are under the threshold of € 20,000, it is accepted that strong evidence exists for adoption of the new therapy.

The available data from the medical records did not allow the quality of life to be measured. Nevertheless, the impact of a potential utility increase on the cost per QALY can be modelled, as in figure 4. This figure shows that a potential utility increase of 0.06 for those patients who were treated effectively with lamotrigine would result in an additional cost per QALY gained of € 15,897. According to the aforementioned threshold, the cost-utility analysis from the healthcare perspective shows strong evidence for the adoption of lamotrigine, provided that lamotrigine therapy would actually increase baseline utility by at least 0.06. Relying on data from medical literature and our own experience, we believe that an increase of 0.06 utility is an appropriate estimation. Messori et al. used a time-trade-off method to value health states of patients with epilepsy (23). According to these data, a patient treated effectively (i.e. 50% reduction in seizure frequency) gained an increase in utility of at least 0.13. Forbes et al. used the EuroQol-5D Health State instrument, and found that for a 50% reduction in seizure

frequency a mean gain in health could reasonably be valued at 0.17 utility extra (24). We sought to reproduce these data and used the EuroQol–5D Health State instrument to measure the quality of life in three subgroups of patients with epilepsy (data not published): patients with complete seizure freedom (n=12), patients with a partial response (decrease in seizure frequency by at least 50%; n=8) and patients with no response to antiepileptic drug therapy (n=7). Seizure–free patients had a mean utility of 0.76 ± 0.11, for partial responders it was 0.70 ± 0.15 and for non–responders 0.55 ± 0.13. According to these assumptions, add–on lamotrigine therapy is an efficient therapy for patients with refractory epilepsy. No data are available on a gain in health for patients who suffer from antiepileptic drug side effects.

Crucial to the acceptance of the outcome of this study is that observational design, with its fortes and drawbacks, be acknowledged as a valid scientific tool. A strong point of the design is that actual utilisation data are collected and analysed, whereas a disadvantage of an economic evaluation piggybacked to a clinical trial is the occurrence of protocol–driven costs (25). Furthermore, observational design enabled us to continue the collection of data from patients who had not been treated effectively with lamotrigine for the full study period. The economic evaluation followed the intention–to–treat principle. Data missing because of patient withdrawal from a clinical trial before reaching the scheduled end date cause a well–known problem in data analysis (26). This study presents population–based data. In a former study, we demonstrated that the baseline characteristics of this Dutch population–based cohort differ from those reported in clinical trials, with respect to age, concurrent use of specific antiepileptic drugs, and length of follow–up (27). This might be explained by the use of lamotrigine in a broader population of epilepsy patients than in add–on lamotrigine regulatory trials. In our study, we included patients with less severe epilepsy, and newly diagnosed patients starting with lamotrigine because of intolerable side effects from their previous treatment, rather than inadequate seizure control. As a consequence, data from the present study reflects the outcome of lamotrigine therapy in daily practice more reliably than clinical trials do.

With regard to weaknesses, the non–blinded and non–controlled design allowed for selection bias and confounding variables that could have occurred in the evaluation of the effectiveness of lamotrigine (28). The fact that this is an uncontrolled study would bias the results in the case of spontaneous improvement of the epilepsy situation of the patients occurring (i.e. regression to the mean). Although the course of epilepsy is variable and improvements could have occurred without any special intervention, we believe that, given the characteristics of our cohort and the length of the study period, the considerable degree of effectiveness seen in year +1 cannot entirely be attributed to regression to the mean.

We used a mirror–image design (patients serving as their own control) instead of a control group, a study method previously used to evaluate the cost–effectiveness of

clozapine, a new antipsychotic drug (29). Physicians start lamotrigine at the peak of disease activity, either an unacceptable seizure frequency or intolerable side effects. This may result in a higher utilisation of hospital services or diagnostic procedures in year –1. However, if only the utilisation of medication was considered (and utilisation of hospital services or diagnostic procedures ignored) an ICER of € 1,042 was obtained, compared to an ICER of € 954 if all cost sources were included. This indicates that there was not much difference regarding the utilisation of hospital services or diagnostic procedures between year +1 and year –1.

For the cost analysis, a healthcare perspective was chosen by us in which all direct costs are recorded. In general, a societal perspective is preferred, nevertheless, there is recognition that the use of other perspectives is acceptable (21). Cost items that are missing in our study include non–medical costs, such as loss of productivity, transportation and paid or unpaid care for patients (7). There is no reason to believe that these costs are likely to be higher for year +1 than for year –1. On the contrary, there is convincing evidence that increasing the effectiveness of epilepsy treatment is the most important contributor to a change in quality of life and a reduction in cost (3;30).

CONCLUSION

Therapeutic options should be available for epilepsy patients with varying needs, including those with persistently high seizure frequencies and those with unacceptable side effects. Several drugs should be listed in case add–on therapy is mandated or the quality of life is adversely affected by the initial selections. These new drugs, like lamotrigine, should not be incorporated without an assessment of their value compared to current standards or acceptable options. In the first year, add–on lamotrigine therapy was effective in 47% of the patients who had uncontrolled epilepsy, the additional cost per successfully treated patient in our study was € 954 annually per patient. Results from the CUA model indicate that lamotrigine could be adopted as an efficient therapy for patients with refractory epilepsy.

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3.4

The validity of using pharmacy records for assessing the retention time of drug therapy

ABSTRACT

Objective

The retention time of drug use reflects a therapy's effectiveness. Electronic prescription records as available from pharmacies, for example, are often used to determine the retention time. The validity of this approach has rarely been assessed.

Aim of this study is establishing the validity of electronic pharmacy data for the assessment of the retention time of lamotrigine, a new antiepileptic drug.

Methods

Events that determine the retention time of lamotrigine are 1) the discontinuation and 2) the addition of another antiepileptic drug. The retention time is the time period between the start of therapy and the occurrence of one of these end points. For 216 patients, we compared the retention time in the pharmacy records with the retention time according to the treating neurologist's records. In addition, the optimal time window for assessment of the end point discontinuation was determined by means of a receiver operator characteristics (ROC) curve.

Results

The positive predictive value of the discontinuation criterion was 96.7%. For the addition criterion, we found a positive predictive value of 62.5%. The lamotrigine retention time assessed from pharmacy records correlated well ($r = 0.91$) with the retention time derived from medical records. The ROC curve showed an optimal interval of 80 days for the discontinuation criterion.

Discussion

Pharmacy records can be used validly to establish the retention time of drug therapy and are a valuable tool in pharmacoepidemiology.

INTRODUCTION

A long retention time with drug therapy is generally desirable for persons with chronic diseases. Retention time is closely related to persistence. Retention time is the duration of continuous treatment with a given drug; persistence reflects the percentage of patients still using the drug after a certain period of time since start of treatment. In 1995, Andrade et al. showed that discontinuation rates of lipid–lowering drugs in clinical practice were much higher than those seen in randomised controlled trials (1). Their landmark publication is important for two reasons. First, the results of their study should be regarded as a word of caution with respect to the generalisability of

randomised controlled trials for daily clinical practice. The well–controlled circumstances under which randomised controlled trials are conducted make the strategies available to patients to adhere to therapy and to manage drug side effects usually more extensive than those available in routine clinical practice (1). Second, Andrade et al. have demonstrated that databases with information on drug prescriptions as available from pharmacies or health insurance providers can be used with relative ease to estimate the continuity of medication use as well as changes in therapy for large, population–based cohorts in a standardised way and without the problem of recall bias (2). Since 1995, persistence in daily practice with medication of various therapeutic classes intended for long–term use has increasingly been assessed with such databases (3–7). These studies have consistently showed that the real–life retention time in drug therapy is considerably lower than could have been assumed from randomised controlled trial data, with persistence rates of various drugs of less than 50% after several years of follow–up. Information on drug–retention time from automated databases can be of value for physicians, healthcare providers and decision–makers, provided that this information is valid. The condition that the retention time of drug therapy is accurately reflected by automated databases has, however, hardly been addressed in literature.

This study evaluates the validity of pharmacy records in estimating the retention time of lamotrigine, a new antiepileptic drug that has been available in the Netherlands from 1997 onwards. For that purpose, we have compared information on lamotrigine use obtained from pharmacy databases with information from medical records of the treating neurologist.

METHODS

This study is part of a project to asses the effectiveness of lamotrigine in daily practice. The present study details the validity of pharmacy data with regard to the determination of the retention time of lamotrigine use and the events associated therewith, namely:

- discontinuation of lamotrigine therapy;
- addition of another antiepileptic drug to lamotrigine therapy.

In most studies on persistence, the event that determines the retention time is the discontinuation of the drug of interest, that is either the discontinuation of any drug intended for the disease concerned or switching to a different drug. However, in the case of antiepileptic drugs, sudden withdrawal can result in severe worsening of seizures. Therefore, another antiepileptic drug is often first added on and the existing therapy is subsequently tapered off (8). Furthermore, as monotherapy often fails in patients with refractory epilepsy, antiepileptic drugs are added in order to enhance the treatment

outcome for these pxatients using polytherapy. In this case, the addition of another antiepileptic drug reflects inadequate seizure control. For this reason we included addition as an event that determines retention time.

Study population

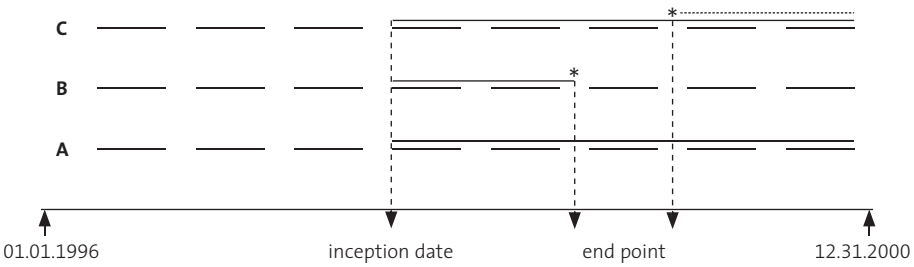
Anonymous prescription data was available from 1,056 community pharmacies (approximately 65% of all pharmacies in the Netherlands). From those pharmacies the drug–dispensing histories for the period of January 1996 to December 2000 were collected from all incidental lamotrigine users. An incidental user was defined as a patient who received the first lamotrigine prescription after a one–year run–in period from 1 January 1996. This resulted in a database with all prescription data of 3,598 incidental users, as previously described in detail (7). The database provided information on the following domains: the patient (age, date of birth, postal code), the drug (trade–name, ATC–classification, Defined Daily Doses (9)) and the prescription (dispensing date, number of units dispensed, prescribed daily dose). A random selection of lamotrigine–using patients (n = 1,819) was asked, through their community pharmacist, to give their written approval for use of their medical record of the treating neurologist for this study. The details of this recruitment procedure have been described elsewhere (10). In brief, the criterion for inclusion of subjects in this study was that medical records and pharmacy records both comprise at least the first year before and after the start of lamotrigine use. The medical records of 360 subjects were reviewed. However, during the reviewing process, data from 144 subjects was excluded for various reasons (lack of information (n=85), unconfirmed diagnosis of epilepsy (n=27), and other reasons (n=32)), leaving 216 patients included in the present study.

Pharmacy data

For each prescription the theoretical duration of drug use according to the pharmacy records was calculated, using information about the dispensing date, the number of units dispensed and the prescribed daily dose. In the Netherlands medicines are dispensed for a maximum of 90 days, with the exception of oral contraceptives. An observation window for each patient was defined as the time between the date of the first prescription of any drug and theoretical end date of the last prescription for any drug during the study period. The three study criteria were defined as follows (figure 1):

1. Discontinuation of lamotrigine therapy: more than 180 days between the theoretical end date of the last lamotrigine prescription and the end of the observation window;
2. Addition of another antiepileptic drug: after the initiation of the lamotrigine therapy, with at least one other prescription of lamotrigine after the start of the other antiepileptic drug;

Figure 1. End points of lamotrigine therapy



Information from all prescriptions (observation window, dash line) and lamotrigine prescriptions (solid line) was used to define patterns of use.
A: continuation of lamotrigine;
B: discontinuation of lamotrigine (more than 180 days between the theoretical end date of the last prescription of lamotrigine and the end of the observation window);
C: addition (dotted line): of another antiepileptic drug after the start of lamotrigine.
Retention time of lamotrigine use is defined as the time between the inception date and the occurrence of one of the two end points or end of the observation window, whichever came first.

3. Retention time: the sum of the theoretical durations of the consecutive lamotrigine prescriptions until one of the aforementioned end points.

Medical records of the treating neurologist

The retrieved information from the medical records on drug use concerned drug name, prescribed daily dose and the dates of initiation and termination of antiepileptic drugs. Medical records were verified for the start date of lamotrigine and for the occurrence of the discontinuation and addition end points. The retention time was calculated as the time between the initiation of lamotrigine and the occurrence of one of the two events. In addition, the reasons for discontinuation and addition were extracted from the medical record.

Data analysis

Data from the pharmacy records and the medical records of 216 subjects was incorporated in a study database in SPSS 11.5. Several aspects of drug exposure according to the pharmacy records were analysed in order to assess the validity of these records.

Validity of using pharmacy records with respect to retention time

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for the two end points discontinuation and addition. The relation between the retention time of lamotrigine estimated from the pharmacy records and the retention time determined from the medical records was evaluated using Pearson's correlations measure.

Table 1. Validity parameters

Pharmacy records	Medical records		N	Validity
	Discontinuation +	Discontinuation –	Total	Sensitivity : 78.4%
Discontinuation +	29	1	30	Specificity : 99.4%
Discontinuation –	8	178	186	PPV : 96.7%
Total numbers	37	179	216	NPV : 95.7%
	Addition +	Addition –		Sensitivity : 83.3%
Addition +	15	9	24	Specificity : 95.5%
Addition –	3	189	192	PPV : 62.5%
Total numbers	18	198	216	NPV : 98.5%
Both endpoints	Endpoint present	Endpoints absent		Sensitivity : 77.3%
Endpoint present	41	9	50	Specificity : 94.5%
Endpoints absent	12	154	166	PPV : 82.0%
Total numbers	53	163	216	NPV : 92.8%

PPV: positive predictive value; NPV: negative predictive value.

Optimisation of discontinuation criterion

Discontinuation of lamotrigine on the basis of pharmacy records was defined at the outset as an interval of at least 180 days between the theoretical end date of the last lamotrigine prescription and the end of the observation window. This time window was optimised by means of a ROC curve, using various cut–off points for the duration between the theoretical end date of the last lamotrigine prescription and the end of the observation window as the 'diagnostic test'.

Reported reasons for changing lamotrigine therapy

The reasons underlying both end points (discontinuation and addition) were investigated. Possible reasons were insufficient effect and/or the occurrence of adverse effects. Our assumptions were that discontinuation was primarily related to adverse effects of lamotrigine and that addition was primarily related to insufficient effect.

RESULTS

The data from pharmacy records and hospital medical records of 216 first–time users of lamotrigine was included in this study. The median age was 43.5 years (range 18 – 84), with a male–female ratio of 39%–61%. Duration of follow–up ranged from 1 to 4 years (mean 1.8 y). The median duration of a lamotrigine prescription was 58.3 days.

Figure 2. Retention time: correlation between electronic prescription data and medical records

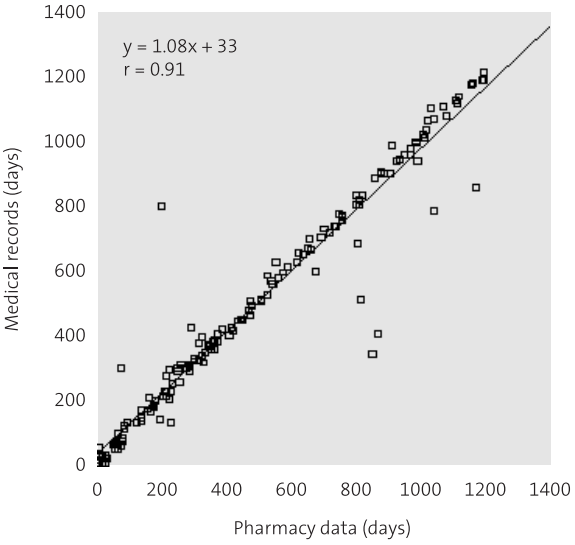
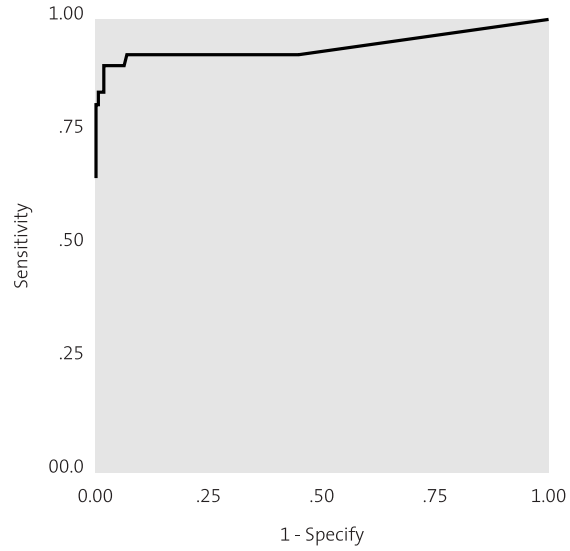


Table 1 presents the validity parameters data for the two end points (discontinuation and addition). For 29 of the 37 patients who discontinued lamotrigine therapy according to the medical record, this event (determined by the 180–day interval) could also be assessed on the basis of pharmacy records (sensitivity 78.4%). Specificity, positive predictive value (PPV) and negative predictive value (NPV) were 99.4%, 96.7% 95.7% respectively. The sensitivity of the addition criterion was 83.3%. Specificity, positive predictive value (PPV) and negative predictive value (NPV) were 99.5%, 62.5% and 98.5% respectively. The correlation between the retention time determined from pharmacy records and from medical records was good (Pearson r = 0.91; figure 2).

The ROC curve used to determine the optimal interval for the discontinuation criterion is presented in Figure 3. The interval defined at the outset of 180 days between the date of the last prescription of lamotrigine and the end of the observation window resulted in a sensitivity of 78% and a specificity of 99%. The optimal interval proved to be 80 days. This resulted in a sensitivity of 92%, a specificity of 97%, PPV 94.4% and NPV 98.3%.

The occurrence of adverse effects was the predominant reason (51%) for discontinuation of lamotrigine (table 2). In 50% of the patients for whom another antiepileptic drug was added, the reason was insufficient efficacy of lamotrigine. Therapy discontinuation occurred sooner than antiepileptic drug addition, mean time to event being 180 and 399 days respectively ($p < 0.05$).

Figure 3. ROC curve for the time between the end of lamotrigine and the end of the observation window as a criterion for discontinuation of lamotrigine



Positive if ≥ .. days	Sensitivity	1 – Specificity
0	1.00	1.00
40	.919	.223
80	**.919**	**.073**
120	.838	.022
160	.838	.011
180	**.784**	**.006**
200	.743	.006
365	.622	.000
730	.189	.000
1095	.054	.000

DISCUSSION

This study demonstrates that pharmacy data is valid as a tool for population–based persistence studies. For both end points together, 80% was confirmed after reviewing the medical records of the treating neurologists. Andrade et al. used the same criterion and found similar results in their validation study: a PPV of 80% (11). For the addition criterion, which is specific for antiepileptic drugs and not used in other studies (see "Methods"), the PPV was substantially lower. If the maximum interval between two subsequent prescriptions of a specific drug was less than 180 days in the pharmacy database, we registered this as ongoing use. This interval may be too crude, and as a result underestimation of discontinuation of antiepileptic drugs could have occurred. Possibly, an antiepileptic drug could be discontinued and a restarted again within the timespan of 180 days, which may be an explanation for the relative low PPV we found for the addition criterion.

The chosen interval of 180 days used to determine discontinuation of lamotrigine therapy was based on an underestimation of the discontinuation frequency. Application of the optimal interval of 80 days (i.e. 40% more than the average prescription duration) resulted in a better estimation of the true frequency of discontinuation.

As expected, discontinuation of therapy was predominantly seen in patients who suffered from adverse effects of lamotrigine. Discontinuation of therapy was

Table 2. Reported reason for changing lamotrigine treatment

	Discontinuation (n = 37)		Addition (n = 18)	
Reason for change in lamotrigine therapy, n				
insufficient efficacy	10	(27%)	9	(50%)
occurrence of adverse events	19	(51%)	2	(11%)
unknown	8	(22 %)	7	(39%)
Time to change in lamotrigine therapy (days)				
mean ± SD†	180 ± 148		399 ± 294	
range	8 – 473		6 – 1,071	
early change (≤ 6 weeks after start LTG), n	6	(20%)	1	(4.2%)

† $p < 0.05$

effectuated earlier than addition of a second antiepileptic drug. Lamotrigine has to be titrated carefully to minimise the risk of severe, idiosyncratic adverse effects. An effect of lamotrigine treatment is not to be expected in the first months of treatment. This probably explains the differences in the time patterns of both end points a finding in line with a study on antipsychotic drugs (12).

An aspect that we were not able to evaluate was whether the validity of pharmacy data is influenced by patients not complying with drug taking. Recently, Tobi et al. have showed that in community pharmacies 99.5% of the prescriptions issued by physicians are claimed within one month (13). Refill compliance, although not similar to actual daily adherence to a drug, can be seen as a valid proxy for compliance.

We have demonstrated the validity of pharmacy data in studying drug retention time. Benefits of pharmacy data include that it is population–based and represents large populations typical of daily clinical practice (6). The data has already been collected and computerised for administrative purposes; therefore, retention–time analyses can be performed relatively quickly and inexpensively. Nevertheless, retention–time studies using only pharmacy data have several limitations. Important, demographic or disease–related, baseline characteristics are lacking. These factors may be associated with drug retention time and also drug preference. Moreover, pharmacy data lacks information on reasons for changing the therapy (e.g. lack of effectiveness, side effects). This information is essential for the full appraisal of the retention–time concept. As pharmacy records and medical records can be seen as complementary with respect to the aspects mentioned above, an approach that uses the benefits of both data sources is to be preferred in the post–marketing assessment of drug therapy. Ideally, record linkage of different automated databases would provide information from the different domains needed to evaluate the retention time of drug therapy rapidly, efficiently and validly.

CONCLUSION

The retention time of prescription drugs is an indication of the success of the therapeutic goal. Studies in a population–based setting are an important way of monitoring this success. The conclusion of this study is that pharmacy records are a valid way of measuring the discontinuation, addition and retention time of drugs, and are therefore a valuable tool in pharmacoepidemiology.

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Dutch neurologists' view on cost and prescription guidelines in the treatment of patients with epilepsy

4.1

ABSTRACT

Objective

To be able to stem the rising cost of the treatment of epilepsy the Dutch Health Care Insurance Board (CVZ) used a new instrument for the first time in the Netherlands: prescription guidelines. The antiepileptic drug lamotrigine, a newcomer on the market in 1995, would only be refunded if prescribed according to a prescription guideline. This article describes the results of a survey held among Dutch neurologists to evaluate the implementation and assessment of this guideline.

Methods

A survey was designed by the Nijmegen Epilepsy Research Group and sent to all 490 members of the Dutch Society for Neurology.

Results

A total of 232 neurologists (51%) responded. Of the 232 respondents, 51 (22%) were familiar with the guideline. Of these 51 neurologists, 80% subscribe either completely or largely to the guideline. A majority of neurologists (77%) favoured guidelines developed by the the medical profession. None of the respondents preferred a guideline that was unconditionally binding. 135 Neurologists agreed upon taken cost into consideration in the development of protocols, 67 neurologists disagreed.

Discussion

From the results of this survey the conclusion may be drawn that the guideline is insufficiently well-known and that adherence is also insufficient. Both this survey and literature show that support for a guideline for the treatment of epilepsy does exist. Furthermore, a majority of the responding neurologists feel that such a guideline may take cost into account, but that the effectiveness of the treatment must always be their primary concern. For the acceptance of a guideline it is important that it be drawn up by members of the profession.

INTRODUCTION

In the past few decades the Dutch government has been trying to rein in the fast-rising cost of public health care. With an average annual rise of ten percent the cost of medication is the fastest rising cost component in the Dutch health care system (1). In order to arrest these rising costs, the government has developed the Drug Refund System and is encouraging the use of formularies.

One particular new development is that for medicine to be refunded it must be prescribed according to a prescription guideline. Through the use of prescription guidelines, authorities try to impose restrictions on the claim made for the drug (2). These restrictions usually relate to follow a treatment guideline, in order to limit the range of prescribers or to limit the range of indications. In the Netherlands this measure was first introduced in 1997 for the antiepileptic drug lamotrigine. When this drug was registered in the Netherlands in 1995, it was initially not included in the Drug Refund System. The then Public Health Care Council (which in 1999 became the CVZ, Dutch Health Care Insurance Board) gave two reasons for this: first, there was insufficient evidence of the added value of lamotrigine over existing antiepileptic medication; and second, lamotrigine cost approximately five times as much as the existing antiepileptic agents. The stalemate on the refunding of lamotrigine was resolved in August 1997, when the Public Health Care Council introduced the Lamotrigine Prescription Guideline. The essence of the guideline is that lamotrigine is reimbursed only for the indication of refractory epilepsy. In the guideline, refractory epilepsy was described as insufficient seizure control after treatment with at least three conventional drugs. The Health Care Insurance Board developed the Lamotrigine Prescription Guideline in co-operation with one independent neurologist and presented it to the Netherlands Association for Neurology. The guideline was then sent to all the Dutch neurologists. The same guideline was applied for the refunding of the antiepileptic drugs that were subsequently introduced, i.e. topiramate, gabapentin and levetiracetam.

It is unclear to what extent the guideline has been accepted and applied in medical practice. This is important to know because it may show to what extent such prescription guidelines may be used in future. This article describes the results of a survey held among Dutch neurologists to evaluate the implementation and assessment of this guideline. The Lamotrigine Prescription Guideline was designed to contain costs by restricting lamotrigine to the (smaller) group of patients with refractory epilepsy. The central question in the survey is: how large is the support for cost containment in such a matter among members of the profession. Finally, possible implications of the results will be discussed.

METHODS

The four-part survey was designed by the Nijmegen Epilepsy Research Group and the department of Medical Technology Assessment of the UMC Nijmegen. The first part asked for general information about the responding neurologist (e.g. practice type, number of epilepsy patients seen weekly others). The second part questioned whether the respondent was aware of the guideline and whether the neurologist adapted the guideline. The third part inquired about the respondents general attitude towards

Table 1. The questions and answers from the survey on protocols

Do you generally follow protocols that are intended for your profession?	Yes	95%	No	4%	Not applicable	2%
Protocols are needed for the treatment of epilepsy	I agree	93%	No opinion	5%	I disagree	2%
Who should develop these protocols?	Profession	77%	CVZ	0.4%	By joint effort	23%
Do you believe protocols should be general enough to be used without the registered indication?	Yes	35%	Yes, if used under the responsibility of a doctor	54%	No	11%
Is cost something you consider in your treatment of individual epilepsy patients?	Never	34%	Occasionally	52%	Always	14%
In developing protocols effectiveness should be considered as well as cost	I agree	58%	No opinion	13%	I disagree	29%
Which way do you prefer to use protocols?	As an advice	86%	I will deviate only for a good reason	14%	As binding	0%
Who should evaluate the guideline?	Profession 83%	CVZ 0.4%	Profession & CVZ 3%	Independent group 12%	No evaluation necessary	2%

protocols for the treatment of epilepsy. Finally, the fourth part offered the opportunity for comments.

The survey was sent to all 490 members of the Dutch Society for Neurology (on the basis of the January 2002 address list). Six weeks after the first mailing a reminder was sent to non-responding neurologists.

Data Analysis

In order to assess any possible bias because of non-response, respondents and non-respondents were compared on gender, and practice type. Any significance between respondents and non-respondents was analysed by means of the Chi-square test.

RESULTS

A total of 232 neurologists (51%) responded. There were no significant differences between the demographical data and the nature of the practices (academic hospital, general hospital and epilepsy centre) between respondents and non-respondents.

The average age of the male respondents was 49, that of the female respondents 46. A neurologist working in an epilepsy centre sees an average of 49 epilepsy patients a week, whereas neurologists in academic and general hospitals only see nine.

Awareness, acceptance and application of the Lamotrigine Prescription Guideline

Of the 232 respondents, 51 (22%) were familiar with the guideline. Of these 51 neurologists, 80% subscribe either completely or largely to the guideline. The main reasons given by those that know the guideline but do not adapt it are (1) "not properly tailored to the individual patient", (2) "too stringent" and (3) "intrinsically wrong" .

Neurologists opinions on the content, development and evaluation of guidelines

The respondents' answers are shown in table 1. The respondents were almost unanimous about the need for guidelines for the treatment of epilepsy: 93% are in favour of a guideline, leaving 5% with no opinion and 2% against. Moreover, 95% of the respondents indicated that they actually would adhere to the guideline in their practice. In answer to the question who they thought should develop these guidelines, 77% answered the medical profession and 23% the medical profession together with the CVZ. Only one respondent (0.4%) preferred to see the CVZ as sole developer. Regarding the evaluation of guidelines, 83% chose the medical profession and 12% an independent study group. In answer to the question how strictly the guideline should be followed, 86% said they felt it should be of an advisory nature and 14% felt it should be mandatory, albeit with the possibility of deviating for good reasons. None of the respondents preferred a guideline that was unconditionally binding.

Opinions are divided about the role cost play in the treatment of epilepsy patients. Of the respondents 34% claim never to consider the cost of treatment, 53% claim to do so sometimes and 14% to do so always. The question whether cost should be taken into consideration in the development of protocols was answered affirmatively by 58% of the entire group of respondents and negatively by 29%, leaving 13% with no opinion.

50 Respondents made use of the opportunity to add comments and remarks in this section of the survey. Thirty–one of these neurologists remarked that cost plays a part, but only if the effect of the treatment is not compromised, whereas nine stated that cost is never a consideration. One–fifth of the comments was of a different and broad–ranging nature.

Remarks and comments

Finally, the respondents were given the opportunity to add their own comments about the prescription guideline and the role of cost within the treatment of epilepsy patients. The 54 remarks could be divided into several categories, which are listed in table 2.

Table 2. A selection of comments and remarks

Category	Number of reactions	Typical comment
Effectiveness and side-effects first	14	"In a protocol it should be: effectiveness first and cost second."
New drugs	14	"The guidelines became outdated when the new drugs topiramate, gabapentin and levetiracetam appeared on the market."
Netherlands Society of Neurologists	12	"(...) let the NVN draw up and evaluate protocols."
Protocol is unknown	11	"As I am not familiar with the protocol and am generally serious about my mail, it might be concluded that there is something wrong with the way the protocol was distributed."
Content	11	"Phenytoin is not the best choice for primary epilepsy."
Positive	5	"I thought it was an excellent protocol, only its use has now become limited."

DISCUSSION

It may be concluded from the results of this survey that the guideline was known by less than a quarter of Dutch neurologists. Several reviews on the effectiveness of clinical guidelines in general show that a guideline's success depends on three factors: (1) awareness of it, (2) having been involved with its development and (3) acceptance of it (3–7).

Regarding awareness of the guideline, it is clear that the target group is insufficiently aware of its existence and contents. Generally speaking, passive distribution is not an effective way to introduce a guideline, regardless of its importance or its explicitness (3,4). The lamotrigine prescription guideline was distributed only once and no enquiry was later made into how well it was known. A more active role of the CVZ and the health care insurers in publicising the guideline might have helped to make it better known.

The second aspect of making a guideline succeed is the extent to which a target group feels involved with such a directive. The effectiveness of a guideline is very positively influenced if the experts among the target group are involved with developing it (5–7). The respondents also have a marked preference for a guideline that is developed by the profession itself.

Acceptance is the third point. Results show that 92% of the respondents feel the need for guidelines when treating epilepsy and that 94% of them actually do follow guidelines in their daily practice. However, the respondents to this survey indicated that their main need is for a guideline that aims primarily for effectiveness. The fact that only one of the respondents prefers a guideline to be developed by the Health Care Insurance Board alone might be accounted for by the difference in viewpoint between

the Health Care Insurance Board (whose main concern was cost containment) and medical specialists (whose concern is patient care only).

It does seem possible to develop a guideline for epilepsy that combines content and cost. After all, the results of this survey among Dutch neurologists show that 52% of the respondents sometimes take cost into account when treating an individual patient and that 13% always do. The sharply rising cost of medication and medical interventions in general appears to have led to a heightened awareness of the importance of cost containment (8). A survey among 800 neurologists in the United States showed that 75% of the respondents are prepared to take cost into account (9). A different US survey, in which 1,000 doctors were sent a questionnaire on cost and cost effectiveness, showed that 84% of the respondents agreed with a guideline that took cost into account (10). The response percentages of these two surveys were 44% and 52% respectively.

As for many conditions, little information exists for epilepsy about important economic issues such as the cost of treatment programs, the possibility of achieving similar clinical outcomes at lower cost or the cost–effectiveness of new treatments (11). This information is needed to use health care resources more efficiently., and this information should be incorporated in adequate guidelines. Adherence to a prescription guideline based on cost containment only will be poor. Guidelines addressing the issues of effectiveness and cost and allowing room to tailor the treatment of epilepsy patients to the individual patients needs are needed.

CONCLUSION

This survey has made it clear how great the support is among neurologists for guidelines in general and for those regarding epilepsy in particular. Both this survey and the literature show that there is support for the idea of taking cost into account when guidelines are developed, but that the effectiveness of the various drugs should remian the main consideration. It is important for the adherence to guidelines that the viewpoint of the profession is taken into account when these guidelines are drawn up and that members of the profession themselves are involved in the process. When the 1997 prescription guideline was drawn up, there was insufficient use of existing know–how in the field of guideline implementation.

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Non-compliance on the part of the professional community with a national guideline: an argumentative policy analysis

4.2

ABSTRACT

Objective

In 1997, the National Health Insurance Board of the Netherlands (College voor Zorgverzekeraars, CVZ) introduced a guideline for the use of a new anti-epileptic drug, lamotrigine. The goal was to limit the use of this relatively expensive drug to patients with difficult-to-treat epilepsy. A survey had shown that only a minority of neurologists were familiar with the guideline, and even fewer applied it in practice. The aim of this study is to identify the contents of the interpretative frames of policy makers and members of the target population.

Methods

The method of reconstructing interpretative frames was used to elicit problem definitions, possible solutions, background theories and preferences. Data were collected by anonymous semi-structured interviews with a representative of the policy-making institute and with seven members of the target group.

Results

The results indicate that the problem definitions of policy makers and practising neurologists differed widely, and that the policy measure conflicted with certain professional beliefs. In such cases, the theory of argumentative policy predicts that policy is unlikely to succeed, unless policy makers take action to ensure a greater congruence in interpretative frames between themselves and their target population.

Discussion

This study shows that interviews with a limited number of neurologists allowed the reconstruction of that part of their interpretative frames that are relevant to the issue and the usage of novel anti-epileptic drugs.

INTRODUCTION

The intractable problems associated with the implementation of public policy are well known (1–3). On the basis of an analysis of the nature and causes of these problems, policy makers have argued that policy should be conceived as an instance of co-production between policy makers and the target population (4,5). A key feature of this argumentative policy theory is the acknowledgement that different stakeholders may define policy problems quite differently, which may lead to different and sometimes opposing appreciations of proposed solutions. Differences in problem definition may, in turn, be related to differences in theoretical backgrounds and preferred ways of

social organisation. Such ensembles are usually referred to as 'appreciative system' or 'interpretative frame' (6,7). In this concept of policy, it is crucial to identify the target population (Whose co-operation is necessary to make this policy successful?) and to identify their interpretative frames (How do they define the problem and how does this relate to other elements of their appreciative system?). Argumentative policy theory predicts that when there is evidence of insufficient congruence in problem definition between policy makers and target population, implementation is likely to fail. In order to succeed, policy should also be directed towards achieving better congruence in problem definition. In other words, it should also be aimed at inducing a process of social learning. This may require adjustment on the part of policy makers, target population, or both, and may entail reconsideration of policy options, evaluation criteria, or underlying assumptions and preferences (8).

In this study, we present the results of an argumentative policy analysis of a specific health-care policy, enacted by the National Health Insurance Board in the Netherlands. This board is an advisory body to the Ministry of Health on coverage issues. In 1997 it issued a guideline for the use of a novel anti-epileptic drug, lamotrigine. The Lamotrigine Prescription Guideline was distributed among all registered neurologists in the Netherlands. This initiative was taken because the costs of the new drug were substantially higher than that of conventional drugs, while there was no clear evidence that lamotrigine had a stronger anti-epileptic effect. The gist of the guideline was that the novel drug should be prescribed only to patients who show insufficient response or unacceptable side effects to (combinations of) conventional drugs. The guideline was issued to prevent lamotrigine from substituting conventional anti-epileptic drugs on a wide scale, with cost control as a major motive. From a survey among neurologists, we found that the policy measure had been largely ineffective: only a minority (22 %) of the respondents knew the guideline, and an even smaller proportion approved of its content and put it into practice (9). The aim of this study was to identify the contents of the interpretative frames of policy makers and members of the target population. On the basis of this material, we discuss whether more congruence in interpretative frames should have been sought, and how this might have been done.

METHODS

The method of reconstructing interpretative frames was used to elicit problem definitions, possible solutions, background theories and preferences (10). Data were collected by anonymous semi-structured interviews with a representative of the policy-making institute and with members of the target population (seven prescribing neurologists engaged in the treatment of patients with epilepsy). One neurologist was employed in a teaching hospital, one was employed in both a teaching and a general

hospital, three neurologists were employed in general hospitals, and two neurologists were employed in tertiary centres, specialised in treatment for patients with epilepsy. Two neurologists were also involved in the development of a broader guideline on the clinical management of patients with epilepsy, to be issued by the Dutch Society of Neurology.

In the interviews, questioning focussed on perceived problems and reasons for actions or decisions concerning care for patients with epilepsy. All interviews were taped, summarised, and coded, with a distinction being made between four layers of interpretative frames: appreciation of solutions, definition of problems, theoretical backgrounds, and normative preferences. Respondent validation was conducted by sending a summary and interpretation of each interview to the respondent for correction. All respondents received an overview of results from all other interviews. Finally, a summary was given of the key problem definitions, possible solutions, background theories, and preferences according to (1) the policy maker, (2) neurologists working in a general hospital, (3) neurologists working in a tertiary centre, (4) neurologists working in a teaching hospital, and (5) neurologists participating in the guideline of the society. Triangulation was conducted by checking findings from interviews with literature and documents.

RESULTS

The reconstructed interpretative frames of the respondents are presented in table 1.

Policy maker

To the policy maker, the guideline was a means with which to prevent neurologists from prescribing lamotrigine to patients for whom a similar seizure control could be achieved at lesser cost with conventional anti–epileptic drugs. The problem stems from a fixed health–care budget on the one hand, and the continuous development of novel health technologies on the other, for which funding is sought. Also, the problem had been anticipated because, more generally, physicians are thought to be inclined to prescribe novel drugs to an extent that may not be supported by scientific evidence, so encouraged by manufacturers. A crucial aspect of the policy maker's theoretical background was the notion that the majority of patients with epilepsy can be adequately treated with conventional drugs. An important aspect of the policy maker's appreciative system was that an efficient use of public resources justifies restrictions on professional autonomy.

Table 1. Summary of reconstructed interpretative frames

Actor	(Judgement towards) solutions	Problem definition	Theoretical backgrounds	Preferences
Policy maker	• Guideline is appropriate instrument to define reimbursement conditions for a new drug	• How to control costs when novel, expensive technologies continue to be developed?	• Health care professionals easily adopt novel technologies • Conventional AEDs are sufficient for the majority of patients with epilepsy	• Don't spend public money on services that perform marginally better at substantially higher costs
Neurologist general hospital	• Guideline does not address problem of my practice	• Little 'hands-on' experience with lamotrigine • Lamotrigine difficult in use	• New drugs are not always better than existing ones • Most patients can be treated successfully with conventional AEDs • Relation between volume and quality of care	• Safety • Patients with refractory epilepsy should be treated in specialised centres
Neurologist tertiary centres	• Therapeutic repertoire should not be unduly restricted	• Selecting best therapy for each patient individually (search carefully by trial and error) • Conventional AEDs are far from optimal (toxicity)	• Incomplete seizure control incurs considerable costs to the patient and to society at large	• Safety • Professional autonomy • Acting in the best interest of the individual patient • Don't stop searching for better treatment modalities
Neurologist teaching hospital		• Little attention to long-term toxicity	• Patients experience seizure control and side effects differently	• Patients' quality of life
Neurologist involved in NVN guideline	• Trials should be conducted that have greater relevance to daily practice	• Evidence from trials not applicable to clinical practice	• Knowledge on research methodology	• Health care should be evidence based • Guideline development is a professional responsibility • Guidelines should be regularly updated

AEDs: antiepeleptic drugs. NVN: Dutch Society of Neurology

Neurologists

None of the respondents were aware that the prescription of lamotrigine should be in accordance with the CVZ guideline in order to obtain reimbursement from health–insurance companies. Neurologists reported that their key problem was finding, for the individual patient, the optimal (combination of) anti–epileptic drugs, and finding this optimal drug regimen as quickly as possible without inflicting unnecessary harm. To them, there are two aspects that determine optimality: seizure control and side effects. The optimum may vary among patients, as patients respond differently to drugs, and because they experience seizure control and the various side effects differently. Moreover, the optimum may not be stable over time: side effects may become apparent only after a prolonged period of time, acceptance of side effects or seizures may change, or drug effectiveness may decrease or may be affected by concurrent events, such as pregnancy. These aspects are the major challenge for the clinician, and anything that helps to achieve the optimal treatment strategy will be welcomed. A guideline restricting the use of a novel anti–epileptic drug on the basis of its costs is not one of them. Costs were not an issue, or, to be more accurate, costs were defined differently. To neurologists, costs are incurred as long as no seizure control is achieved, without acceptable side effects. In this context, costs are defined more broadly, in terms of unpredictability, interference with daily life, and costs of self–inflicted harm (resulting from seizures) to the patient and his family. Although not quantified, they are considered to outweigh the costs of drug treatment.

Apart from this commonality, there were certain differences between neurologists working in general hospitals and those working in teaching hospitals or specialised centres.

Neurologists working in general hospitals

Interestingly, the novelty of the anti–epileptic drug lamotrigine was mentioned as a major problem by neurologists working in general hospitals. Inevitably, because of its novelty, relatively little is known, especially about the safety profile of the drug. Although trials have been published, the medical profession has had little opportunity to obtain experiential knowledge. This was considered particularly relevant, since earlier drugs that had been introduced on the basis of trial results had turned out to be inferior to the then available drugs in terms of safety and effectiveness. One respondent remarked:

"Some drugs promised to be very good; however, they turned out to have many side effects, which holds true for vigabatrin, or were not as effective as promised, for example gabapentine" (respondent N2, interview)

Respondents also considered lamotrigine relatively difficult in its daily use, since its dosage needs to be gradually increased in order to prevent rash. In general, neurologists thought that lamotrigine is not more effective than conventional drugs. They also emphasised that in general hospitals, patients are treated who have uncomplicated

epilepsy. Neurologists, in general, found no need to treat these patients with novel drugs, nor a justification to do so, in view of the limited knowledge about these drugs. Patients with more complicated epilepsy are referred to tertiary centres, specialised in care for epilepsy. As such, respondents considered it inappropriate to examine drug effects in this group of patients, and not part of their professional responsibility.

Neurologists working in tertiary or teaching hospitals

In patients with more complex types of epilepsy, finding the best treatment is a process of trial and error: "Predominantly, you follow the textbooks, but sometimes you try drugs or combinations of them as presented at conferences. Sometimes it is an improvement, sometimes not." (respondent N5, interview)

Respondents considered the toxicity profile of lamotrigine an advantage, as well as its lesser potential for interaction with other drugs. Furthermore, they had observed a positive psychotropic effect of lamotrigine, which was sometimes an additional reason for prescribing it. An objection of these neurologists to the guideline of the National Health Insurance Board was that it was too static. "New anti-epileptic drugs are missing, the guideline is not updated [...] Opportunities for evaluation of the treatment protocol should be incorporated." (respondent N4, interview)

Neurologist involved in guideline development

An additional problem that was mentioned by the neurologist who was involved in the development of the guideline by the Dutch Society of Neurology was that evidence from trials does not always translate easily into clinical practice. The purpose of trials is to support the registration of a new drug on the basis of its efficacy and safety. Because of differences in study populations and patients seen in daily practice, the generalisability of trial findings may be limited. According to this respondent, the National Health Insurance Board should support the conducting of naturalistic trials, to assist the professional community in finding the value of new drugs in daily practice.

With respect to costs, the respondent pointed out the arbitrariness of health-care policy. Why should the use of lamotrigine be restricted on efficiency grounds, while many treatments are covered that have never been assessed for their efficiency? Clearly, to this respondent, consistency in health-care policy was an important element in his appreciative system.

DISCUSSION

This study shows that interviews with a limited number of neurologists allowed for the reconstruction of part of their interpretative frames that are relevant to the issue of the usage of novel anti-epileptic drugs. This resulted in information that is important to the policy maker in a number of ways:

First, the target population turned out to be heterogeneous. Neurologists working in general hospitals differed from neurologists working in teaching hospitals or specialised centres in a way that should be taken into account when devising policy measures.

Second, little ground appeared to exist to assume that neurologists would start prescribing the new anti-epileptic drug on a wide scale.

Third, neurologists experience other problems in their treatment of patients with epilepsy. The National Health Insurance Board might assist in resolving these problems, thereby realising its own policy objectives: optimisation of quality and efficiency of health care.

The gist of the guideline issued by the National Health Insurance Board was: try to achieve seizure control without incurring serious side effects, using (combinations of) conventional anti-epileptic drugs. The reason for this recommendation was cost control. Interestingly, the recommended strategy is common practice among neurologists working in general hospitals. The rationale, however, is different: they consider the novel drug not particularly easy to use, and, more importantly, they have learned in the past that novel drugs, although approved by national agencies, need not always be better than existing ones. Their professional ethic prohibits neurologists from experimenting with new drugs when the annual number of patients seen in their practice is too small. This may be especially true of patients with epilepsy, with whom achieving seizure control without incurring side effects is notoriously difficult. For neurologists working in teaching hospitals or specialised centres, however, the guideline was largely irrelevant. They treat patients with refractory epilepsy only; attempts to achieve seizure control with conventional drugs had already been made and were unsuccessful.

The type of problems neurologists experience in their management of patients with epilepsy is related to the unpredictability of responses of individual patients to various treatments. The challenge, then, is to find the optimal treatment for each individual patient as quickly as possible. Data from published trials are relevant to this purpose, but only to a limited extent: study populations may, and often do, differ from patients seen in daily practice, and treatment protocols may be a-typical (11). It would be helpful, therefore, to conduct more naturalistic studies (12) and to conduct N of 1 trials (13). Also, the setting-up of central registries, where unexpected events can be reported when treating patients with anti-epileptic drugs, would help to identify possible side-effects at an earliest possible stage, since trials have not always been found to constitute a reliable source for this type of information (14).

The National Health Insurance Board might consider ways of assisting or encouraging the professional community to introduce such measures, e.g. by co–funding naturalistic trials (which are unlikely to be funded by manufacturers) or by covering the costs of setting up N of 1 trial facilities or central registries.

The study has, of course, certain limitations. There may be other areas where physicians are more likely to adopt novel drugs. Policy makers should, therefore, examine this aspect for each case individually. Also, it cannot be excluded that in other general hospitals neurologists will not refer patients who fail to respond to conventional drugs to specialised centres. However, on the basis of our results, it would be justified to stipulate that novel drugs be used exclusively in specialised centres. When policy institutes help funding naturalistic trials and setting up research facilities, it would not be unreasonable to demand that they are involved in deciding whether novel drugs should continue to be used in specialised centres or may be released for general usage. Such a role would be more appropriate than developing and distributing a guideline, which – according to the respondents in this study – should be left to the professional community.

This case study supports the idea that it is important to establish at an early stage of policy development how the target populations of policy measures experience problems and which solutions appear sensible to them. The investment that this requires in terms of funds and human resources is almost certainly modest compared to the costs of (repeated) health policy failures.

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4.3

A cost-effectiveness decision model for antiepileptic drug treatment in newly diagnosed epilepsy patients

ABSTRACT

Objective

To establish the cost–effectiveness of antiepileptic drug treatment strategies of newly diagnosed patients with epilepsy.

Methods

A decision analysis was carried out comparing effectiveness and treatment cost of six treatment strategies comprising carbamazepine, lamotrigine and valproate as first–line and second–line drugs. Three outcome groups were defined: complete success, partial success and failure. Data on seizure control and failure due to adverse effects were derived from the literature. Data on resource use, costs and quality of life were collected for each outcome group by means of a patient survey.

Results

Cost and quality of life data were obtained from 71 patients. Cost increased and quality of life decreased from complete success to failure outcome groups. The probability of obtaining complete success varied from 64% (VPA–CBZ strategy) to 74% (LTG–VPA strategy). The strategy LTG–VPA was more effective than the least expensive strategy CBZ–VPA, but at higher costs per additional effectively treated patient. Probabilistic sensitivity analysis confirmed the conclusions based on calculations not taking uncertainty into account. Subsequent analysis showed that changing inclusion criteria used in the selection of the studies from the literature had a major effect on cost–effectiveness ratios of the various strategies. Lamotrigine first–line strategies did not show to be cost–effective. However, lamotrigine second–line strategies can be cost–effective depending on the willingness to pay for patient improvement.

Discussion

Only few studies satisfied our inclusion criteria for employment in our decision model. Our model add to the use of conventional antiepileptic drugs for patients wit newly diagnosed epilepsy. This study illustrates that with the data presently available, decision analysis for antiepileptic drug treatment choice depends on the trials included. Prospective real–life studies are needed in which first and second–line treatment strategies are compared with respect to both effectiveness and costs.

INTRODUCTION

Carbamazepine (CBZ), phenobarbital, phenytoin and valproate (VPA) have been the leading antiepileptic drugs for more than 30 years. Several new antiepileptic drugs have however been introduced during the last decade.

In order to be licensed, these new antiepileptic drugs had to demonstrate efficacy as adjunctive therapy in so-called intractable patients; i.e. in patients with inadequate seizure control despite optimal therapy. Once a new compound is licensed and has demonstrated its effectiveness in daily practice, it will often be compared to existing compounds in monotherapy trials for patients with newly diagnosed epilepsy. Lamotrigine (LTG), one of the new antiepileptic drugs, has been involved in several of these comparative monotherapy trials (1-4). A main advantage of lamotrigine over conventional antiepileptic drugs seems to be its favourable tolerability profile, leading to fewer treatment failures, fewer cognitive side effects and a better disease-related quality of life in patients with newly diagnosed epilepsy (4-6).

These results may contribute to a more widespread use of lamotrigine. However, the acquisition cost of lamotrigine is several times higher than that of conventional antiepileptic drugs. In this era of constrained health care resources, health authorities are beginning to demand economical justification for new antiepileptic drugs. The purpose of this study is to establish the cost-effectiveness of lamotrigine in patients with newly diagnosed epilepsy. In this study the cost-effectiveness of lamotrigine is compared with carbamazepine and valproate through a decision analytic approach. Drug-specific effectiveness data were derived from randomised clinical trials and observational studies published in the international literature. Patient data on cost consumption and health-related quality of life were collected for patients in one out of three different outcome groups via a patient questionnaire.

Six treatment strategies are compared in this study, i.e., carbamazepine first-line monotherapy followed by either valproate or lamotrigine in case carbamazepine fails due to either lack of seizure control or adverse effects, valproate first-line followed by either carbamazepine or lamotrigine in case valproate fails due to either lack of seizure control or adverse effects and lamotrigine first-line monotherapy followed by either carbamazepine or valproate in case lamotrigine fails due to either lack of seizure control or adverse effects.

METHODS

Study Design

This paper details a cost–effectiveness analysis evaluating first and second–line treatment strategies in patients with newly diagnosed epilepsy. The analysis uses a decision tree as a modelling instrument. In accordance with Dutch guidelines on pharmacoeconomic research a societal perspective was adopted for the economic evaluations (7). The time span comprises the first year of treatment.

Decision Tree Model

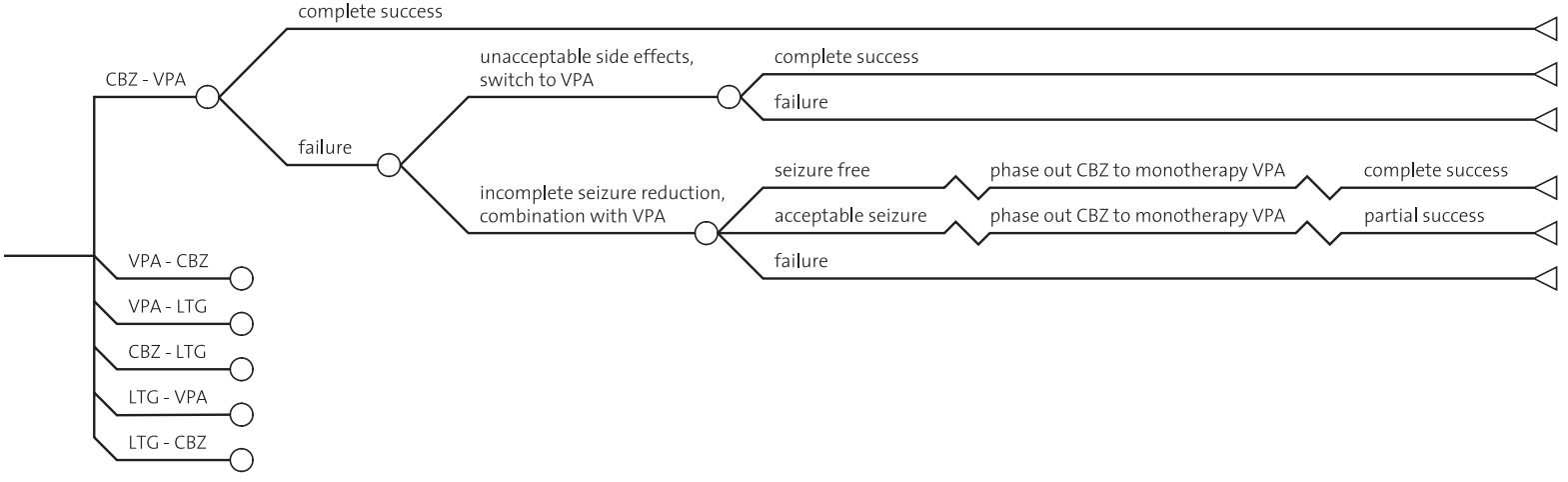
A decision tree analysis (software program DATA; TreeAge Software, Williamstown, MA) was used as a model to depict potential clinical pathways and outcomes within the first year of treatment. Figure 1 shows the structure of the model. Three first–line drugs are studied, carbamazepine, valproate and lamotrigine. Six treatment strategies are evaluated comprising all possible variations of first and second–line treatment with these three agents. In the model the effectiveness of the first drug is evaluated after six months. When a patient is seizure free and does not experience unacceptable adverse effects, the patient continues with the first–line drug for the remaining six months. If there are unacceptable side effects on the first drug, the patient is switched directly to a second drug in monotherapy. In case of inadequate seizure control the second–line treatment is first added to the first–line drug. In this case the first–line drug is withdrawn after two months and second–line monotherapy is used for the last four months of the study. Thus, the assumption is made that at the end of the first year all patients are in one of three outcome groups, i.e. complete success, partial success or failure. Complete success implies the patient being seizure free. Partial success is defined as a reduction in seizure frequency of more than 50% compared with baseline. Failure is defined as inadequate seizure control (i.e. less than 50% seizure reduction) or the occurrence of unacceptable adverse effects.

Decision Model Input

Path probabilities, reflecting the effectiveness of the different treatment strategies, were based upon literature data. A limited number of studies with comparable study designs were selected from the available full–published comparative monotherapy studies. The inclusion criteria used for this selection procedure were:

- study participants had to be over 12 years of age with newly diagnosed epilepsy;
- seizures had to be partial and / or generalised tonic-clonic seizures;
- starting dosages and titration schedules had to be in accordance with present guidelines;
- evaluation period of at least 24 weeks;
- no dose adjustments allowed during evaluation period.

Figure 1. Decision tree model



The model is shown for the first-line strategy carbamazepine followed by valproate in case of failure (CBZ VPA). The structure of the model applies to all strategies. Circles represent chance nodes. Triangles represent outcome groups, in which patients remain for the duration of the first year of treatment.

From the selected studies, first–line probabilities on seizure freedom, failure due to side effects and failure due to insufficient seizure reduction were calculated. All analyses were performed on a per protocol basis. Individual probabilities were based on weighted probabilities from the different studies based on their study size.

Second–line studies were selected from available full–published studies evaluated in two earlier review papers (8;9). The inclusion criteria were:

- titration and taper schedules in accordance with present guidelines;
- combination period of 8 –12 weeks;
- monotherapy phase of 8 –12 weeks.

Collection of data on cost and quality of life

From a societal viewpoint three sectors can be identified in which epilepsy–related costs may occur: health care sector, patient and family sector and others (10). To estimate cost of epilepsy care in the first sector, data were obtained from the medical records of patients. Data on costs in the two latter sectors were collected using patient questionnaires. In this questionnaire information was collected retrospectively over a period of 3 months and prospectively the same data were collected for 6 months following the inclusion date. Three months is a recommended recall period for retrospective data collection, based on validity study of Severens et al (11). Adult epilepsy patients visiting the outpatient department of Neurology of the University Medical Centre Nijmegen and the University Hospital Maastricht could participate. The treating physicians classified each patient into one of the three outcome groups based on seizure frequency. Patients were classified as complete success (seizure free), partial success (more than 50% reduction in seizure frequency) or failure (less then 50% seizure reduction).

The daily maintenance doses defined in the decision model are based on the average doses achieved in the trials considered, i.e. 600 mg for carbamazepine, 150 mg for lamotrigine and 1,000 mg for valproate. For lamotrigine used in combination with carbamazepine the daily dose was set at 300 mg.

Cost Valuation

The assignment of unit cost to the various elements of epilepsy care is based on an instruction document for economic evaluation in Dutch health care by Oostenbrink et al (12). This document provides guideline prices relevant for the Netherlands for various items, such as outpatient clinic visits, hospitalisation et cetera. When there is no guideline price for an item, these items were valued by using official tariff lists for allowable reimbursement rates.

Table 1 mentions these cost units and their prices. All figures were updated to January 2002 according to the rate of inflation. Inflation was measured by the Consumer Price Index published by Statistics Netherlands (http://www.cbs.nl). All costs were expressed in Euro (€).

Table 1. Unit cost per item

Cost item	Cost measure	Unit cost (€)	Source
Health care sector	cost per visit		
GP services	cost per visit	16.7	guideline price
Physician services		46.1	guideline price
Hospital services			
Neurologic ward	cost per admission day	304.3	guideline price
Diagnostics			
Laboratory	cost per procedure	4.4	tariff [a]
Imaging (EEG, CT, MRI)	cost per procedure	95.6	tariff [b]
Drug therapy	cost per month		tariff
CBZ 600 mg		9.7	
LTG 150 mg		69.6	
VPA 1000 mg		15.9	
Patient & family sector			
Unpaid care	cost per hour	8.9	guideline price
Other sectors			
Absence of work	cost per day	106.5	guideline price [c]

[a] Weighted composition of tariffs from different laboratory investigations
[b] Weighted composition of tariffs from different imaging tests
[c] Weigthed composition of different ages

Cost-effectiveness Analysis

The analysis of the decision–tree model results in probabilities of a theoretical patient to end up in one of three outcome groups, i.e. complete success, partial success or failure, the so–called path probabilities. Based on these path probabilities the expected cost of each of the six strategies was determined. General principles of cost–effectiveness analysis were applied to these results (10). First, it was determined whether certain strategies were dominated by other strategies. A dominated strategy is more costly, but less effective than another strategy. For nondominated strategies, the cost–effectiveness analysis combines the expected costs with the probability of complete success, i.e. the incremental cost–effectiveness ratio (ICER). Beginning with the least costly strategy, non–dominated alternatives were compared to calculate incremental ratios.

The ICER is calculated as

$$\frac{[(\text{mean annual cost per patient})_{\text{strategy 2}} - (\text{mean annual cost per patient})_{\text{strategy 1}}]}{[(\text{complete success})_{\text{strategy 2}} - (\text{complete success})_{\text{strategy 1}}]}.$$

Table 2. Studies incorporated into first-line strategies of the decision tree model

Model	AED	Patients	Doses (mg/day)	Starting doses (mg)	Titration	Complete success	Failure due to ADR	Failure due to incomplete control	Reference
A	CBZ	101	600	200	200 mg / 2 weeks	63%	12%	25%	Reunanen (2)
	CBZ	45	Based on plasma levels	Not mentioned	Not mentioned	67%	27%	6%	Kälviäinen (14)
	VPA	97	Flexible	300 mg	No fixed scheme	59%	11%	30%	Christe (15)
	LTG	98	100	25	25 mg / 2 weeks	60%	5%	35%	Reunanen (2)
	LTG	106	200	25	25 mg / 2 weeks	63%	5%	32%	Reunanen (2)
B	CBZ	103	Flexible	200 mg	200 mg / week	48%	34%	18%	Brodie (1)
	LTG	107	Flexible	50 mg	50 mg / week	48%	19%	33%	Brodie (1)
C	CBZ	141	Flexible	200 mg	first: 200 mg /week than: 200 mg / 2 weeks	47%	17%	36%	Richens (18)
	VPA	140	Flexible	400 mg	400 mg / week	44%	6%	50%	Richens (18)

Model B incorporates the studies of model A and B; model C of A and C. Model D (not shown) incorporates all studies.

Table 3. Probabilities of second-line drug strategies

Second-line strategy[1]	Complete success	Partial success	Failure	Number of patients	Comments	Reference
CBZ-VPA and VPA-CBZ	8%	23%	69%	95	Assumption: VPA -> CBZ as CBZ -> VPA	Brodie et al. (23)
CBZ-LTG and LTG-CBZ	22%	21%	57%	63	Assumption: CBZ -> LTG as LTG -> CBZ	Jozwiak et al. (24)
VPA-LTG and LTG-VPA	32%	32%	34%	63	Assumption: VPA -> LTG as LTG -> VPA	Jozwiak et al. (24)
Second AED after failure first AED due to side effects	34%		66%	98	General assumption	Kwan et al. (25)

[1] CBZ-VPA: path probabilities of VPA as second-line drug after failure of CBZ as first-line drug (see Figure 1).

Sensitivity Analysis

Second order uncertainty of the cost–effectiveness estimates of the six strategies was investigated by Monte Carlo simulation techniques. Distributions were defined for the probabilities and costs used in the model (complete success, incomplete seizure reduction, unacceptable side–effects). As probabilities are supposed to have a value between 0 and 1, Beta–distributions were fitted for all these parameters. For costs gamma distributions (zero to infinity) were defined. Of course, the effectiveness measure complete success was dichotomous and assumed to be deterministic and therefore not part of the probabilistic sensitivity analysis. All 6 strategies were evaluated in the simulation that was performed with 1,000 iterations. As a result of the iterations, for every cost and effectiveness pair of a strategy, net benefits were calculated for a range of levels of ceiling cost–effectiveness ratios. For each iteration a strategy is considered optimal in case of the highest net benefit and the proportion of the iterations being optimal is determined for each strategy. Subsequently, cost–effectiveness acceptability curves were drawn for each of the six strategies, showing the cost–effectiveness acceptability frontier in relation to different levels of the ceiling cost–effectiveness ratio (13).

RESULTS

Decision tree analysis

A literature search yielded fourteen first–line monotherapy trials. Only three of these 14 studies met our inclusion criteria (2,14,15). The probabilities for the various outcome groups derived from these studies are presented in table 2. The other studies were excluded for various reasons. Two studies also concerned patients that did not have newly diagnosed epilepsy (6,16). One study only considered patients older than 65 years of age (3). Titration schedules used in two studies were no longer in agreement with present guidelines (1,4). The evaluation period was too short in one study (17). In five studies the number of patients becoming seizure free at the end of the evaluation phase was not mentioned (18–22).

Two second–line studies met our inclusion criteria (23,24). No data were found on probabilities for second–line valproate or carbamazepine after failure of lamotrigine. An assumption was made that these latter probabilities were the same as for second–line lamotrigine after failure of valproate or carbamazepine. No drug specific data were found on the probability of a second drug leading to complete success after failure of a first drug due to side effects. A general probability for this scenario was derived from the observational study by Kwan et al (25). The probabilities for second line treatments are shown in table 3.

Table 4. Patient characteristics

	Complete success	Partial success	Failure
Number of patients	30	27	14
Age (mean years ± SD)	48.5 ± 18.6	42.5 ± 17.6	54.3 ± 20.3
Gender (% male)	70	48	50
QOLIE–31 question 1–30 (mean score ± SD)	74.0 ± 13.9	60.6 ± 16.6	48.6 ± 12.7

SD = standard deviation

Table 5. Average breakdown of costs per patient group in 2 per month (and ranges)

Cost item	Complete success		Partial success		Failure	
Health care sector						
GP services	0	(0–0)	0.5	(0 – 10.7)	4.9	(0 – 46.2)
Physician services	8.5	(0.1 –35.3)	8.3	(0 – 46.2)	13.1	(0.1 – 73.6)
Hospital services	0	(0 – 0)	17.6	(0 – 625.5)	54.6	(0–727.6)
Diagnostics (laboratory & imaging)	24.5	(0.2 – 161.8)	33.8	(0 – 302.2)	41.0	(0.2 – 330.0)
Patient & family sector						
Unpaid care	2.8	(0 - 64.5)	67.4	(0 - 3642.7)	16.8	(0–413.6)
Others						
Absence of work	–		–		–	
subtotal[1]	35.8		127.6		130.4	

[1] The cost of drug therapy is strategy specific and therefore not shown in Table 5.

Table 6. Cost effectiveness analysis

Strategy (model A)	Expected 1–year cost per patient (€)	Expected complete success	Incremental cost effectiveness ratio[1]
CBZ – VPA	975	0.684	Reference
VPA – CBZ	1,111	0.635	(Dominated)
CBZ – LTG[2]	1,230	0.726	6,079
VPA – LTG	1,255	0.722	(Dominated)
LTG – VPA[3]	1,861	0.742	40,422
LTG – CBZ	2,036	0.706	(Dominated)

[1] The ICER is calculated relative to the next less costly nondominated strategy.
[2] Calculation ICER CBZ-LTG : (1230-975)/(0.726-0.684)
[3] Calculation ICER LTG-VPA : (1861-1230)/(0.742-0.726)

Figure 2. Cost-effectiveness plane showing for each of the strategies the results of 1,000 iterations of the Monte Carlo simulation

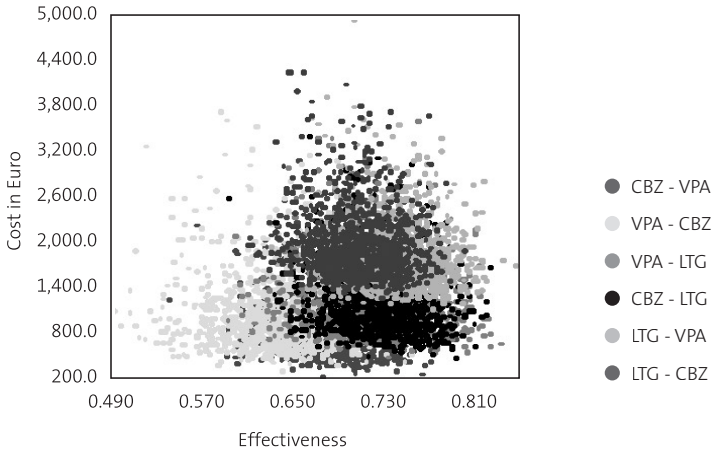
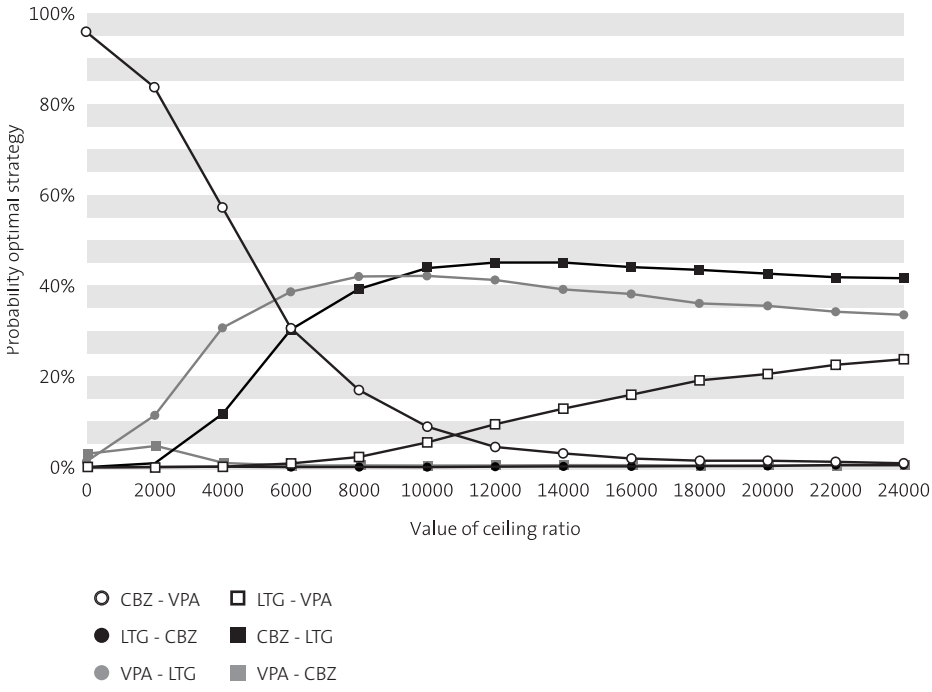


Figure 3. Cost-effectiveness acceptability curves for the decision regarding the most efficient strategy for antiepileptic drug treatment in newly diagnosed epilepsy patients



Collection of data on cost

Self–reported data on cost and quality of life were collected from a total of 71 patients: 30 patients were in the complete success outcome group, 27 patients in the partial success outcome group and 14 patients in the failure outcome group. The patient characteristics are described in table 4. Patients in the complete success outcome group had the highest mean total score on the QOLIE–31 (74.0). Patients in the partial success and the failure outcome group had lower mean scores, 60.6 and 48.6 respectively. Average monthly costs per patient, with the exception of drug costs, are presented in table 5. Overall, an inverse relation between cost consumption per item and outcome groups was demonstrated. Patients in the complete success group appeared to incur the lowest costs (€ 35.8/month) in contrast to patients in the failure outcome group (€ 130.4/month). The items 'hospital services' and 'unpaid care' contributed most to the costs. Lost productivity due to absence of work was negligible.

Cost-effectiveness Analysis

The results of the cost–effectiveness analysis are presented in table 6 and ranked in ascending order of expected costs. The probability of obtaining complete success varied from 64 (VPA–CBZ strategy) to 74% (LTG–VPA). The treatment strategy with the lowest cost, the reference treatment, was CBZ–VPA with expected annual costs per patient for the first year of treatment of € 975 (probability complete success is 68.4%). The treatment strategy LTG–CBZ took up the highest costs, € 2,036 annually. The LTG–CBZ strategy and also the strategies VPA–LTG and VPA–CBZ were dominated strategies (more expensive and less effective). Two treatment alternatives, CBZ–LTG and LTG–VPA, were nondominated strategies. The incremental cost–effectiveness ratio of CBZ–LTG relative to the CBZ–VPA strategy is € 6,079 per additional complete success patient. That of LTG–VPA relative to CBZ–LTG is € 40,422 per additional complete success patient.

Sensitivity Analysis

The results of the probabilistic sensitivity analysis are graphically shown in figure 2. In this figure cost–effectiveness is shown for all six strategies. Figure 3 shows the cost–effectiveness acceptability curves of the different strategies. The CBZ–VPA strategy turns out to have the best probability to make a cost–effective decision. In case society is willingness–to–pay more than € 5,000 per effectively treated patient, strategies including a switch to lamotrigine as a second–line drug become more favourable. The first–line strategies with lamotrigine as a first–line drug are clearly shown not to be cost–effective, despite a high cost–effectiveness threshold of € 25,000 per effectively treated patient. It can be concluded that probabilistic sensitivity analysis confirms the conclusions based on calculations not taking uncertainty into account.

In a subsequent analysis the impact of the selected studies (used for determining first–line path probabilities) on the outcomes of the cost–effectiveness model was

Table 7. Sensitivity of cost effectiveness outcome for studies incorporated into the model

	Model A			Model B			Model C			Model D		
Strategy	**Cost (€)**	**Effect**	**ICER**	**Cost (€)**	**Effect**	**ICER**	**Cost (€)**	**Effect**	**ICER**	**Cost (€)**	**Effect**	**ICER**
CBZ – VPA	975	0.684	Reference	1,038	0.658	Reference	1,050	0.64	Reference	1,126	0.585	Reference
VPA – CBZ	1,111	0.635	(Dominated)	1,102	0.648	(Dominated)	1,270	0.508	(Dominated)	1,271	0.508	(Dominated)
CBZ – LTG	1,230	0.726	6,079	1,297	0.686	(Dominated)	1,332	0.677	7,485	1,449	0.627	7,663
VPA – LTG	1,255	0.722	(Dominated)	1,255	0.723	3,348	1,473	0.621	(Dominated)	1,473	0.621	(Dominated)
LTG – VPA	1,861	0.742	40,422	1,891	0.703	(Dominated)	1,855	0.743	8,021	1,891	0.703	5,876
LTG – CBZ	2,036	0.706	(Dominated)	2,057	0.667	(Dominated)	2,012	0.71	(Dominated)	2,057	0.667	(Dominated)

evaluated. Three additional models were designed that incorporated studies that did not meet the inclusion criteria used for our initial model (which will be called model A from here on). These models are shown in table 7.

In model B a study by Brodie et al. was added (1). This study was not included into model A because titration schedules for both carbamazepine and lamotrigine were not conform present guidelines (26). Incorporation of this study leaves the reference strategy CBZ–VPA unchanged, the strategies CBZ–LTG and LTG–VPA become dominated strategies (where as in model A they were non–dominated strategies).

Model C consists of the studies included in model A plus a study by Richens et al. (18). This study was left out of model A for two reasons. The starting dosage of VPA was rather low compared to present guidelines, and this resulted in a prolonged period before the eventual effect of this drug could be expected. Furthermore, the number of patients becoming seizure free was not clearly mentioned in this study and had to be estimated from a Kaplan–Meier graph. Incorporation of this study leaves the reference strategy unchanged, the ICER of the LTG–VPA strategy becomes € 8,021 (whereas in model A the ICER was € 40,422).

In model D all studies from aforesaid models are included and consequently all first–line path probabilities changed compared to model A. Model D resembled model A, the strategy with the least costs was CBZ–VPA and strategies CBZ–LTG and LTG–VPA were more effective compared to this reference strategy.

DISCUSSION

Ideally, an economic evaluation consists of a real–life study in which both clinical and cost data are assessed (10,27). Such a study is not available for antiepileptic drugs and therefore we used existing published literature for estimates of effectiveness and a patient questionnaire for estimates on cost items. As there is no randomised trial directly comparing carbamazepine, valproate and lamotrigine, a decision model was used for an indirect comparison of a number of original, controlled trials. To strengthen these comparisons stringent inclusion criteria to the eligible trials were applied. This resulted in a limited number of included trials. For the probabilities of second–line treatment we had to rely on several assumptions, since only two studies satisfied our predefined inclusion criteria. In our opinion, it is justified to assume that the effectiveness of carbamazepine and valproate as second–line treatments following lamotrigine is equal to that of lamotrigine used as a second–line treatment following carbamazepine or valproate. One would expect that the total number of patients responding to A, possibly followed by B, is the same as the total number of patients responding to B, possibly followed by A. This is supported by two crossover studies in the literature (28,29),

All models in our study show that CBZ–VPA is the reference treatment and that there are more effective treatments, but at considerable costs per extra patient treated effectively. Assessing levels of certainty is important in cost–effectiveness analysis because of the assumptions made about the relation between the intervention and the outcome (30). This is, however, rather complicated because the outcome in a cost–effectiveness analysis is a ratio of two different outcomes (costs and effects), rather than an estimate of a single outcome (say, adequate seizure reduction). Sensitivity analysis, preferably probabilistic, is an accepted method to evaluate if the result is robust to changes in the different parameters involved. This study shows that it is also important to use transparent inclusion criteria for data used to build the decision tree model. The set of literature data used as input data was of influence on the outcome, especially on the ICER, as the differences between models A–D show. It became clear that the results of cost–effectiveness analyses of first–line antiepileptic drugs monotherapy depend on the included clinical trials.

In this study we used a cost questionnaire to obtain data on cost consumption and quality of life. The validity of a cost questionnaire such as ours was assessed previously (31). This comprehensive questionnaire allows collecting patient–based costs of epilepsy, as is widely recommended for cost–effectiveness studies (32). Another approach to estimate cost items is the use of an expert panel (Delphi panel), as has been employed in previous economic studies in epilepsy (33,34). Such a panel estimates the costs incurred by patients. We believe that patient–based cost collecting is at least as adequate, and gives additional valid data. The cost are assumed to be equal within each of the three outcome categories, except for drug costs. It seems reasonable that the frequency of visits to the outpatient department and of investigations are dependent on the response to treatment, rather than on the drug with which this outcome is realised.

It also is likely that the utility within an outcome category is related to that category, rather than to the drug used.

We found that cost of treatment of patients with newly diagnosed epilepsy was lowest for the conventional strategy CBZ–VPA. The LTG–VPA strategy, with first–line use of lamotrigine, was more effective but against considerably higher cost per individual seizure free patient. The cost–effectiveness of lamotrigine monotherapy was compared to carbamazepine monotherapy in one cost minimisation study and to carbamazepine, phenytoin and valproate monotherapy in a second cost minimisation study (33,34). The first study was based on only one comparative monotherapy trial, while the second study was based on 8 different monotherapy studies. In cost minimisation studies the efficacy of the respective treatments is assumed to be equal; the only outcome is treatment cost per initial strategy and the costs considered are drug costs, costs of resources employed in the management of adverse events, and costs associated with therapeutic switching. Both cost minimisation studies showed that lamotrigine is considerably more expensive for newly diagnosed patients in health service costs incurred. There are several differences

between our study and these two cost minimisation studies: (a): efficacy is not assumed to be equal in our study; (b): we determined costs per additionally effectively treated patient in comparison to the reference treatment; (c): we used stringent inclusion criteria to yield a sample of comparable studies; (d): our sensitivity analysis evaluated the effects of including further studies instead of evaluating best–case and worst–case scenario's of included studies; and (e): we used a patient questionnaire instead of a Delphi panel. Despite differences in methodology between the approaches, the findings are overall rather similar.

In our study we obtained health–related quality of life outcomes from epilepsy patients using the QOLIE–31 questionnaire. Besides this, we were not able to establish a health state utility for our patient population. For a small subgroup Visual Analogue Scale values were measured and these were clearly related to the effect of treatment: for complete success 75.8 (S.D. 16.2), for partial success 70.0 (S.D. 16.3) and 54.8 (S.D. 9.6) for failure. VAS values can be used for calculating utility values and thus perform cost per Quality adjusted life year–calculations. However, in this study the number of patients, respectively 12, 5, and 4 were too small to have valid cost/QALY results. Due to the small sample size of the present study we could not collect treatment strategy–specific data but had to confine the data to three outcome groups. This may have been detrimental to lamotrigine, as lamotrigine offered patients with newly diagnosed epilepsy a better health–related quality of life in clinical trials compared to carbamazepine and valproate (5,35). The small sample size of our study population and the limited data on health–related quality of life available in literature made that we used a conservative approach with seizure frequency as only outcome measure.

Our study results adds to use of conventional antiepileptic drugs as first–line treatment. Our findings agree with the technology appraisal guidance 'newer drugs for epilepsy in adults' from the National Institute for Clinical Excellence (NICE) from the United Kingdom (36). In the NICE guidance the newer antiepileptic drugs like lamotrigine are recommended for the management of epilepsy in people who have not benefited from treatment with the conventional antiepileptic drugs, or for whom the older drugs are unsuitable because of contraindications, interactions, or the person is a woman of childbearing potential.

Our study also illustrates that with the data presently available, decision analysis for drug treatment choice is very dependent on the trials included. Neurologists are counting on cost–effectiveness data in order to make rational choices (37). Therefore there is a need for prospective real–life studies comparing strategies of first and second–line treatment and incorporating both cost and outcomes.

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General discussion

5

INTRODUCTION

In this final chapter the individual studies regarding the value assessment of lamotrigine in daily practice will be put into the broader perspective of the value assessment of new drugs after their approval in general. For a discussion of the shortcomings and merits of the individual studies on the value of lamotrigine the reader is referred to the discussion section of the individual studies.

At the moment of drug approval there is still a high degree of uncertainty about the value of a drug for daily clinical practice (1). This uncertainty applies to all value domains: safety, effectiveness and cost-effectiveness in daily practice (2). This is mainly due to the well known and accepted limitations of drug evaluation before approval. For the purpose of this discussion, the most important limitations include relatively short follow-up and small sample sizes, concern that compliance with the medications in the trial will exceed that in actual practice, different characteristics of patients and clinicians in the trial compared with actual practice (which may influence the efficacy and safety of the drug), poor reporting of side effects and "drug creep" (the tendency for drugs to be used for indications not studied in the trials) (3-5). The limited applicability of premarketing study results to daily practice reveals a "knowledge gap" that is relevant to health-care professionals as well as policy makers. The essence of postmarketing drug evaluation is to bridge this gap by increasing the amount of knowledge needed to make rational therapy decisions on an individual patient level as well as for populations. What the most sensible and efficient method is to bridge this gap is still unclear (1;6). At least three different study types can be used to evaluate new drugs and to rationalise drug policy (table 1): (1) randomised trials to determine efficacy and safety (which are required for approval) and (1a) real-world randomised, or pragmatic, trials to determine effectiveness and safety in regular practice; (2) decision analysis models; (3) prospective observational studies with targeted data collection and (3a) retrospective observational studies that use data collected routinely as part of the treatment process.

In our approach to assess the value of a new drug, we used observational study methodologies in chapters 2 (prescription databases) and 3 (targeted data collection). A decision analysis model is presented in chapter 4. In our approach we addressed the value domains effectiveness and cost-effectiveness but not the value domain safety.

THE POSITIONING OF NEW DRUGS USING EXISTING DATA (CHAPTER 2)

The position of a new drug within the therapeutic arsenal reflects its value in daily practice. Information on the incidence of drug use over time provides insight into the uptake of a new drug from the moment of market introduction and reflects the perceived effectiveness by prescribers and patients. Information on the retention time

Table 1. Study designs used in the assessment of new drugs

Type of study	Purpose	Timing	Usual sponsor(s)	Strengths	Weaknesses
Randomised trial	Determines drug efficacy and safety, usually compared with placebo	Before licensing	Industry	Provides unbiased evidence about efficacy Detects major side effects	Real-world effectiveness may not be reflected Important but rare side effects may not be detected New drug is often not compared with commonly used alternatives
Pragmatic trials	Determines drug effectiveness and side effects in the real world	Before and after licensing	Industry Health Insurance Board Granting agencies	Provides evidence about real-world effectiveness and side effects of the drug, compared to usual practice	Comparator treatments are often not standardised Large sample sizes are often required
Decision analysis model	Provides comparative estimates on cost and effectiveness of drugs	Before and after licensing	Health Insurance Board Industry	Provides a flexible and timely workframe for analysis	Validity of the model is questionable because model input is based on assumptions or expert opinion
Observational study	Provides detailed information about patient characteristics and outcomes	After licensing	Health Insurance Board Granting agencies Industry	Provides detailed information about clinical relevance Can combine information with administrative data	Data collection can be time-consuming, especially if large sample size needed If not randomised, biases can make determination of causation difficult
Observational study with data already collected	Evaluates drug use, compliance, use of concomitant drugs, and the association between drug use and outcomes in the real world	After licensing	Health Insurance Board Granting agencies Industry	Is relatively inexpensive and fast Can be population-based Can detect rare side effects	Databases often lack detailed information needed to characterise patients or determine outcome Determination of causation is difficult because of biases resulting from lack of randomisation

Modified from Laupacis et al. (46).

(i.e. persistence) of a drug reflects its general effectiveness in daily practice over time. In chapter 2 the computerised registration of dispensed prescription drugs formed the cornerstone for population-based research on the positioning of lamotrigine. Prescription databases represent one of the most accurate means of measuring drug exposure as they do not suffer from recall bias and are virtually complete (6-9). The large prescription databases used in this thesis provide a relatively easy, inexpensive and rapid way of collecting information on drug use for a large number of patients. Furthermore, the link between the drugs prescribed and the prescribing physician offers the opportunity to examine patterns of drug use as well as prescribing patterns, as is done in chapter 2 sub 3.

In chapter 2, three important aspects in the positioning of a new drug are addressed: (1) diffusion, (2) persistence and (3) selective prescribing.

Diffusion of a new drug in daily practice

The position of a new drug is subject to change after approval for use, because the drug suddenly becomes available for a much broader population of patients with regard to factors like demographics, disease severity and indication of use. This diffusion process has consequences for the market share of a new drug, therefore we studied the cost impact of a new drug in chapter 2 sub 2. The diffusion process of lamotrigine has been studied in chapter 2 sub 3. Most of the variance in the rate of diffusion of an innovation, from 49 to 87 per cent, can, according to the diffusion theory of Rogers, be explained by five attributes (10):

1. Relative advantage: the degree to which an innovation is perceived as being better than the idea it supersedes;
2. Compatibility: the degree to which an innovation is perceived as being consistent with existing values, past experiences and needs of potential adapters;
3. Complexity: the degree to which an innovation is perceived as difficult to understand and use;
4. Trialability: the degree to which an innovation may be experimented with on a limited basis;
5. Observability: the degree to which the results of an innovation are visible to others.

In addition to these attributes of an innovation, other variables, such as the extent of the pharmaceutical company's promotion efforts, affect an innovation's rate of diffusion (10-12).

Opinion leaders are able to classify new drugs as innovative, semi-innovative or me-too drugs. The diffusion rates of innovative and me-too drugs in daily practice differ; nevertheless, drugs that are not considered to be innovative may still reach high diffusion rates (11;12).

The resultant of all the aforementioned factors that influence diffusion can be evaluated with databases of prescription records. These databases, however, lack important information to elucidate this process fully. For instance, prescription databases cannot adequately evaluate the impact of commercial influence, an essential component that is found to lower the barriers of adoption of semi-innovative drugs (13).

Persistence use of a new drug

Measuring patient persistency with drug therapy provides valuable information concerning the overall effectiveness of a drug in daily practice (14). Analysing automated records of prescriptions actually filled, as is done in chapter 2 sub 4, makes it possible to use a standardised measure from pharmacy data to define continuity of medication use and gaps in therapy. Although a prescription filled is not identical to a drug consumed, patterns of ongoing prescription filling represent an accurate way of estimating actual medication use in large populations (15). In chapter 3 sub.4 we showed that the structured form in which pharmacy data are registered allows for the valid measurement of persistence of drug use.

Disappointing persistence rates with long-term medication of various classes are found in daily practice (16-18). Low drug persistence can contribute substantially to the variability observed in the therapeutic outcome of drugs, i.e. the number needed for treatment may increase substantially and thus can markedly lessen the cost-effectiveness of these drugs in daily practice. This should be considered as a word of caution that results obtained in daily clinical practice may differ substantially from those of randomised clinical trials. On the other hand, it is important to bear in mind the limitations of pharmacy databases. These databases lack potentially important information about the reason for prescribing, the physician's rationale regarding changes in treatment decisions and baseline characteristics of the patient related to the outcome of therapy. Furthermore, it is important to realise that ongoing drug use, measured accurately using prescription data, is not necessarily equivalent to effective drug treatment, as is illustrated in chapter 3 sub.2.

Selective prescribing

An important consideration in the assessment of a drug's position in daily practice is that new drugs may be prescribed predominantly to patients with severe disease due to various factors, like normal human behaviour of physicians, treatment guidelines or marketing strategies (19). Selective prescribing is a general phenomenon that has been described for various classes of drugs; it should be considered a special form of allocation bias, as interventions are given to patients with large prognostic differences (20-22). Selective prescribing may have important consequences for the validity of observational studies if this aspect remains unrecognised in their analysis (20).

Ways to account for imbalances in baseline characteristics pertaining to the outcome are stratification of the patients in subgroups for these characteristics and adjusting for the differences in the analysis by multivariable techniques such as multiple logistic regression. Relatively newer techniques such as modelling propensity scores have shown to be valuable alternatives (23). For the outcome studies in this thesis (chapter 3.sub 2 & 3sub.3) the selection of control patients was avoided by using patients as their own control, which was done by comparing different periods of each patient's medical history (20).

Value assessment of new drugs with existing data

The potential of prescription databases in the value assessment of new drugs is related to the fact that these data can be obtained on a population-base level, are relatively inexpensive and almost real-time available (table 1). At present, however, the potential of these data for use in health-economics and health-services research is hampered because detailed information from several domains (e.g. disease-, prescriber- and patient-related domains) is missing. The strengths of pharmacy data are enhanced if their weaknesses are overcome. The key to this is population-based record linkage of pharmacy data with other routine health data that is stored electronically, e.g. clinical data, diagnostic data or administrative data (24;25). At present, there is a lot of work to be done to overcome validity issues related to difficulties in identifying and extracting data, and the lack of uniformity in coding systems, definitions and data structure (25;26). Observational studies that use linked databases can play a key role in drug evaluation after regulatory approval. Some of the research questions (regarding the value of new drugs) posed by health technology assessment through randomised controlled trials can indeed be answered using this approach (25).

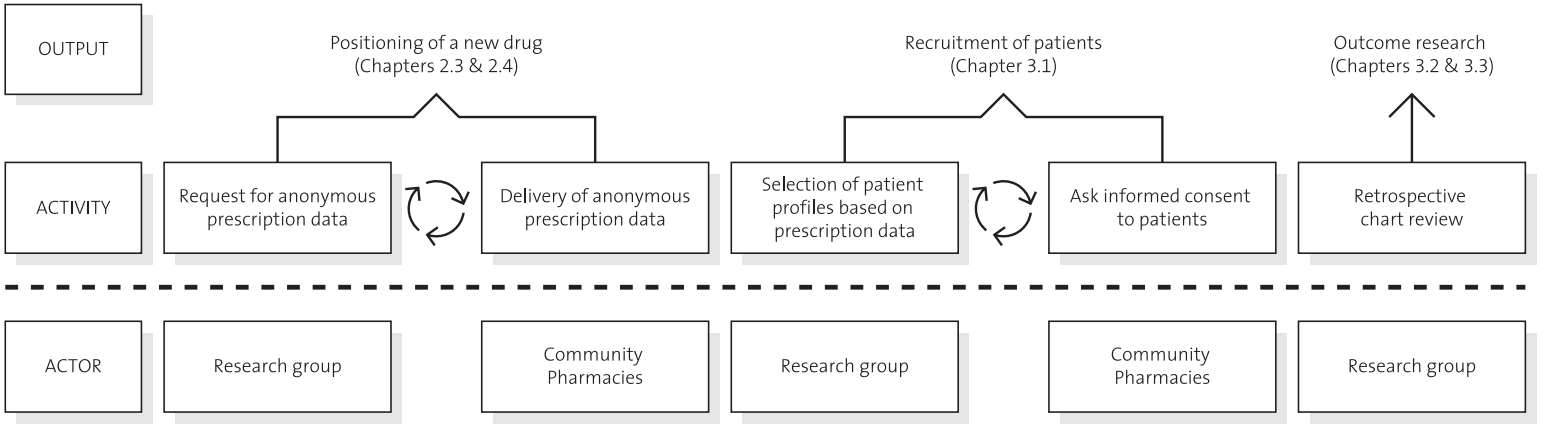
VALUE ASSESSMENT OF NEW DRUGS USING TARGETED DATA COLLECTION (CHAPTER 3)

We have proposed an observational model with targeted data collection for outcome research regarding the effectiveness of a new drug in daily practice. The proposed model is presented in figure 1, the different generic steps of this model are discussed below.

Randomised versus non-randomised

The key step in outcome research is to choose an appropriate design that produces interpretable findings. Our choice to use observational design is based on its lower costs and greater timeliness and because, due to the better generalisability of the results, a broader range of patients could be reached. In the present study design, multiple observations are made within a single group before and after the intervention

Figure 1. Staged approach of the observational study design used in this thesis.



is implemented. In this mirror analysis, the 'control' observations are those made before the intervention is implemented (27). Due to the lack of randomisation, the observational study offers less opportunity to control for biases and confounding factors (28). The principal difference between experimental designs (randomised studies) and observational designs (non-randomised studies) can be characterised as a difference in their susceptibility to selection bias. It could also be argued that with the chosen study design one cannot differentiate a true drug effect from spontaneous variation (1).

Recruitment of a diverse study population

Dutch privacy regulations include the law on persons registries and the law on individual health care agreement (29;30). The first law is a general law applicable to all areas of society and is about how to deal with confidentiality and privacy issues. The second law regulates the relationship between the patient and the health-care provider and how clinical data are kept within the context of individual health care provision. Both legal frameworks need to be considered if one wants to use patient data for research purposes.

The goal of the recruitment step is to gather, within the boundaries of the legal framework, a diverse study population which reflects the range and distribution of patient characteristics, physician characteristics and treatment settings as observed in daily practice. The recruitment of patients from a community-based cohort accommodates this need for diversity, as prescriptions from the various treatment settings are processed at the pharmacy. Using pharmacy data enabled us to apply filter criteria for age, concomitant medication and length of follow-up in the recruitment procedure. Because information is available on eligible subjects who do not participate, it is possible to compare characteristics of participants to non-participants. In addition, we were able to select patients who had already discontinued lamotrigine treatment, because pharmacy data do not suffer from recall bias. However, this advantage was somewhat counteracted because those patients were less likely to give consent (chapter 3.sub1). If patients were recruited prospectively through community pharmacies this might not have been an issue. Another advantage of the recruitment procedure proposed in this thesis, is that recruitment of patients for the study is independent of the initiation of the therapy. These two decisions are not always so distinct in studies conducted after approval where the physician initiates the drug and recruits the patient for evaluation (31). Sometimes such postmarketing studies lack scientific justification and are simply meant to increase sales, i.e. postmarketing seeding studies (32).

We conclude that recruitment of patients for outcome research through community pharmacies complies with existing privacy legislation and that it is pragmatic and efficient.

Measuring health outcomes

It is preferable that a broad set of relevant health outcomes is measured in the final step of outcome research. The selection of the outcomes to be measured is based on the most important anticipated effects of the intervention, taking into account those outcomes that are of the greatest relevance to the prescribers and the health-policy decision makers. This means that ideally the outcomes should include functional end points (like quality of life, satisfaction, compliance and costs) as well as the traditional end points (like effect on disease, adverse effects, morbidity and mortality) (33). In this case, the retrospective chart review proved to be the Achilles' heel of the study. A considerable number of cases had to be excluded from the analysis, because the chart did not contain sufficient information to assess the effect of the lamotrigine intervention on the traditional end point of seizure reduction, let alone that information on functional end points was available.

Observational design in value assessment

A dilemma remains the interpretation of the cost-effectiveness ratio obtained from observational studies, as a comparator group using a reference drug is either lacking or prone to bias. The vulnerability of retrospective, observational studies is that they depend on information that primarily serves a different goal (the registration of treatment aspects of an individual patient). Although it may seem odd that outcome information like seizure frequency is not consequently registered, this is frequently the case. In Chapter 4, sub 3 we showed that data on functional end points can be obtained with the use of a (cost) diary. Information on these end points can be obtained retrospectively with the items from this diary, but validity decreases if the recall period is more than two to three months (34). Therefore information on both traditional and functional end points is best obtained if these data are collected prospectively. The observational data could be used to validate and to enrich the findings of observational studies using administrative databases.

CLINICAL AND HEALTH-POLICY DECISION MAKING (CHAPTER 4)

Rising drug costs and constraints in health-care budget have inspired the growing interest in clinical and health-policy decision making. Traditional cost-containment measures, like reference price systems, co-payment and reduction of the number of reimbursed drugs through the use of positive and negative lists, proved to be only partially successful (35). Recently three parallel trends were started in the Netherlands to establish incentives for efficient health-care delivery:

1. More decentralisation of drug policy responsibilities; e.g. the Dutch government considers giving the local health insurers the responsibility for the purchasing process for drugs;
2. Usage of prescription restrictions;
3. Usage of health economic analysis by reimbursement authorities (35;36).

Use of prescription guidelines (chapters 4.sub 1 & 2)

While reimbursement decisions traditionally applied to the officially registered indication, authorities like the Dutch Health Insurance Board (CVZ) have recently been imposing restrictions on the claim made for the drug (35). This illustrates the fact that total costs are important in the reimbursement decision, along with cost-effectiveness. Total costs are determined by the price of the drug, the total number of patients with the disease for whom the drug has been demonstrated to be efficacious and the number of patients without that disease for whom the drug is prescribed. The last, 'off-label', use is of considerable concern and can be caused by the use of the drug for other diseases or for patients with the same disease that could have benefited from older drugs. Prescription guidelines were developed to influence the use of new drugs, aiming at ensuring that patients who will benefit the most from these drugs will receive them, while at the same time limiting overall expenditure. There is little information available, however, to support the efficacy of prescription guidelines (37).

The first prescription guideline issued by the Dutch Health Insurance Board was not sufficiently implemented in daily practice as can be concluded from chapters 4. sub 1 and 2. Translating guidelines into daily practice is known to be difficult, and even the use in practice of high-quality guidelines is not ensured (38;39). Argumentative policy theory predicts that when there is evidence of insufficient congruence in problem definition between policy makers and health-care professionals (i.e. the target audience), implementation is likely to fail. A physician's clinical decision making is shaped by considerations of medication effectiveness, risk assessment, patient characteristics, drug reimbursement and cost (40). Dissemination and implementation in daily practice of a policy maker's guideline focussing on cost containment solely will not be successful. Whereas guidelines are more likely to be adopted when the clinical context is reflected, professionals are involved and the guidance is based on stable and convincing evidence (41).

Health economic analysis (chapter 4 sub.3)

Demonstration of efficacy, safety and quality of manufacture are currently recognised as the three hurdles that must be overcome in drug approval and the reimbursement process. To help evaluate and contain costs, several jurisdictions have imposed a fourth hurdle, one that requires the demonstration of a drug's cost-effectiveness prior to establishing reimbursement (42). In the Netherlands a formal requirement

for consideration of economic evidence as part of the reimbursement decision was introduced in 2005. It is expected that the reimbursement of a majority of submitted drugs will be based on decision-analysis models (43;44). There are several ways in which modelling may be used in economic evaluations. These include generalising the results (from a clinical trial to clinical practice, or from one geographical location to another), extrapolating from the available data (e.g. beyond the follow-up period of the clinical trial, or to final endpoints based on intermediate endpoints), and synthesising comparisons between treatments in the absence of head-to-head comparisons (43). Despite the increasing use of modelling in economic evaluations, several concerns have been raised. These are related to the inappropriate use of clinical data and the difficulties of extrapolating the data. In chapter 4 sub .3 more general concerns about the transparency or validity of models were raised. This chapter shows that the researcher can frame the model to favour one intervention over another. It is therefore important that (1) All choices and assumptions that form the input for the model are transparently justified in the description of the model; (2) The robustness of the results is tested by undertaking a thorough sensitivity analysis and (3) The findings of model-based economic evaluations are revisited, or updated, as more data become available. Otherwise, decision analysis models will continue to be considered a 'black box' by many people (43).

FUTURE PERSPECTIVES

The gap between the premarketing phase (clinical trials) and daily medical practice has been widely recognised. Clinical research should consistently produce an adequate supply of information to meet the needs of clinical and health-policy decision making, in other words: to close this gap. A strategy that can be applied is the introduction of an interactive, two-stage approach of marketing approval (45;46). In the two-stage appraisal discussed here the initial appraisal is done at the time of market approval, with the second appraisal done at a later date when more is known about the value of the new drug.

Stage 1: Initial approval

An initial appraisal of a new drug is done at the time of market approval. The new drug is reimbursed by default for a pre-determined number of years. This period enables an evaluation of the safety, effectiveness and pharmacoeconomic aspects of the new drug to be made. The initial appraisal is based on the quality of manufacture, efficacy and safety data from the regulatory approval trials and a preliminary cost-effectiveness analysis using decision models. In the initial approval stage a prescription guideline should be made in a joint effort by policy makers (e.g. Health Care Insurance Board) and

health-care professionals (e.g. associations of physicians) to come up with a (mandatory) clinical guideline, which incorporates clinical guidance, health technology and economic aspects of the new drug. The prescription guideline tries to translate the experimental experience with the drug and balances it with uncertainty, evidence and experience with therapeutic alternatives and costs. On the basis of the prescription guideline the new drug becomes available to those who need it, within restricted indications of use.

Stage 2: Second approval

After the initial approval stage data on the outcome of the drug has to be accumulated prospectively, with the use of both routine data collection and targeted data in order to for the second appraisal to be done. The outcome data are provided by patients and providers and contain information on both traditional end points (disease parameters, adverse drug reactions) and functional endpoints (quality of life, cost). At present, postmarketing studies aim at only one value domain, namely safety. It is, however, difficult to make sense of the concept of safety without the vantage point of special patient populations and therapeutic goals (2). Assessments targeting both effectiveness and safety are more informative than those evaluating safety alone. The preferred way to collect these data is by means of an electronic data file, because this provides a rational, standardised method of data collection. An advantage of this approach is that it is more informative than the present postmarketing surveillance of new drugs, which aims at safety data only (2).

During the second stage, the collected data can be analysed with the use of different observational study designs or pragmatic trials. These studies generate evidence on use, effectiveness and safety outcomes and cost, which form the basis for a second approval decision. This decision is best made by a post-marketing body ('centre of excellence') that is independent from the agencies responsible for initial approval and reimbursement. This separation of powers is essential to ensure objectivity and to avoid conflict of interest. The second approval is completed when:

- properly structured effectiveness and economic endpoints have been completed;
- sufficient number of patients have been exposed to detect rare (e.g. 1 in 10,000) adverse drug reactions; and
- the recommended dose has been clearly established (46).

This two-stage approach should create an operational infrastructure in which the value of a drug is assessed and constantly re-assessed (figure 2). The latter aspect, continuous reassessment, is vital to obtain the import goals of this staged approach:

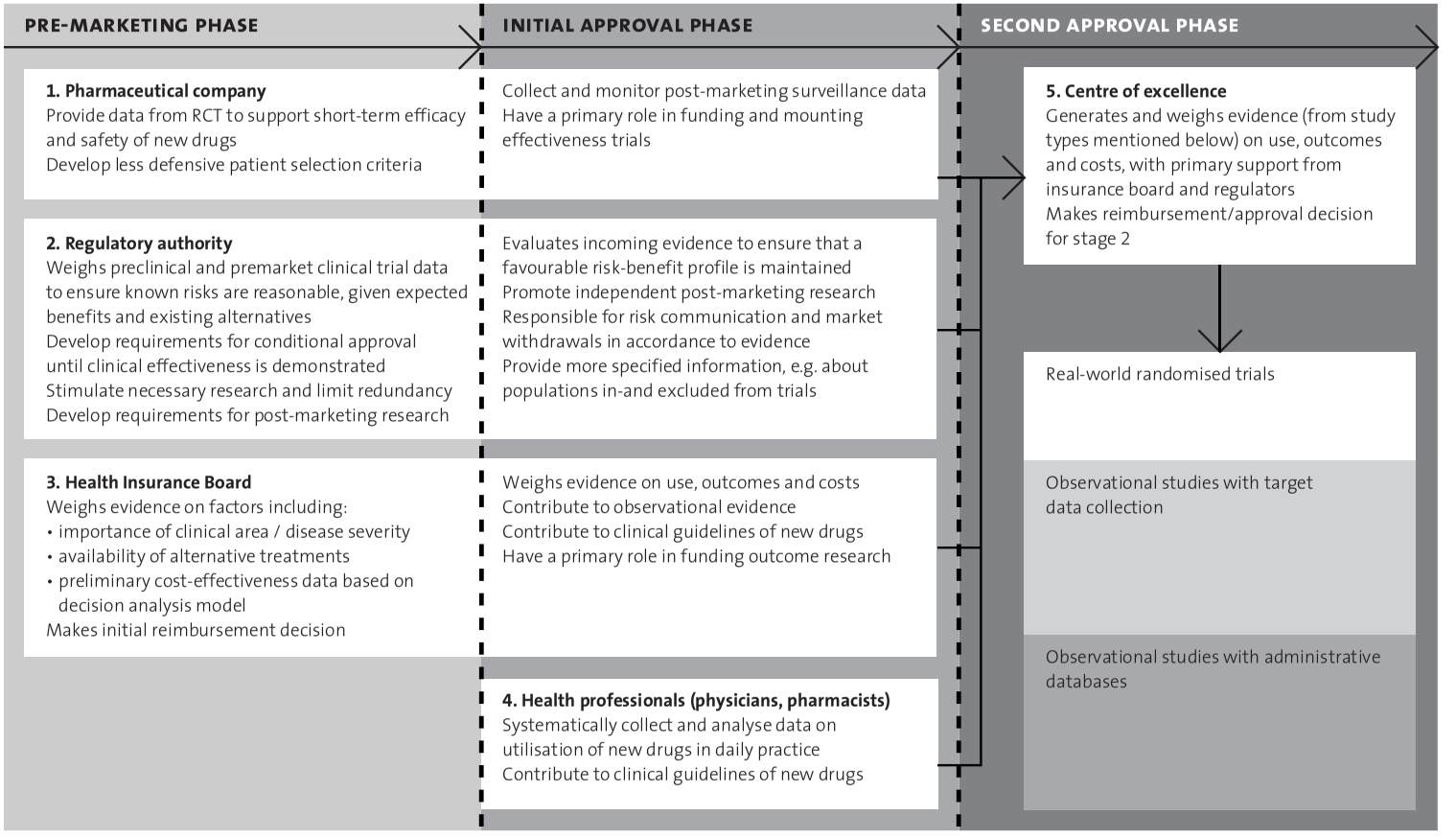
1. Get the evidence to prescribers. The challenge, for regulators and health-policy makers, is to see that the necessary information is developed and disseminated appropriately. As to the greater part of medical interventions, it is broadly acknowledged that physicians do not change their behaviour only on the basis of information

published in journals (5). Additional methods are needed, such as summaries of tailor-made information, simple practice guidelines and audit and feedback. These methods should be used to encourage cost-effective prescribing. The aim is to promote the use of certain drugs for cost-effective indications, as well as discourage the cost-ineffective use of drugs.

2. Evaluate and constantly re-evaluate the evidence. Decisions about the reimbursement of drugs should be made on an ongoing basis. All parties concerned must be fully aware that an initial decision to fund a drug will be regularly re-evaluated and may be reversed. The latter may be the case for a drug with an inappropriately high utilisation in a group of patients in whom its cost-effectiveness has not been established, or the emergence of new information about unexpected side effects (5).

This new strategy will require more investments in research and outcome assessment, and there will be considerable discussion about who should pay for what (47). However, in the end the benefits generated by the more appropriate use of drugs will be considerable, as information about drug effects is an extremely valuable resource for sound therapeutic choices and future product development (2).

Figure 2. A proposed model for connecting pre-marketing clinical research and daily clinical practice



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Appendices

SUMMARY

In this thesis several pharmacoepidemiologic approaches to the value assessment of lamotrigine, a new antiepileptic drug, in daily clinical practice are described. Epilepsy is a neurological disorder characterised by recurrent, unprovoked seizures. The incidence of epilepsy in developed countries has been estimated to be around 50 cases per 100,000 people per year. The severity of the condition and the prognosis vary according to the type of epilepsy. Drug therapy is the mainstay of epilepsy treatment, and the aim is to abolish seizures completely, while keeping the side effects of treatment to a minimum.

The field of antiepileptic drug therapy has been an unusual one, being/having been dominated for decennia by older drugs. These older antiepileptic drugs have several limitations, among them the adverse effects on the central nervous system and other side effects, the potential to interact with numerous drugs and the effects of these drugs on the unborn child.

With the introduction of lamotrigine, in 1995, a new treatment option was offered to patients with epilepsy. A reimbursement decision for lamotrigine was taken almost two years after market approval. The late reimbursement decision was a consequence of the high acquisition cost of lamotrigine and the relative lack of information about up-to-date clinical (added) value at the moment of approval. This deadlock was ended when the Dutch Health Care Insurance Board imposed restrictions on the claim made for the drug. These restrictions were included in a prescribing guideline that was subsequently published. The Lamotrigine Prescription Guideline was the first prescription guideline in the Netherlands aiming at cost containment. The case of lamotrigine, among others, illustrates that registration and reimbursement procedures have become clearly distinct processes.

In this thesis, the value of lamotrigine in daily clinical practice, as well as the implementation of the Lamotrigine Prescription Guideline have been assessed.

In Chapter 1, the scope and objective of this thesis are described. It outlines the thinking about drug evaluation by presenting the four phases of drug evaluation: efficacy, accessibility, effectiveness and cost-effectiveness. Even after marketing approval of a new drug, much is still unknown about the drug, its safety and its effects at the start of use in daily practice. Within this scope, the objective of this thesis was to gain insight in the value of lamotrigine in daily clinical practice using observational study designs.

Chapter 2 comprises four studies describing the positioning of new antiepileptic drugs in general, and lamotrigine in particular. Chapter 2, sub 1 reviews the available, published pharmacological information on the new antiepileptic drugs. The current insights on mechanisms of action, efficacy, effectiveness, adverse effects, pharmacokinetics are discussed, and selection criteria for the appropriate use of the new antiepileptic drugs are presented.

Chapter 2, sub 2 describes the impact new antiepileptic drugs had on the volume and the cost of antiepileptic drugs in the Netherlands during 1995 - 2001. For this study, data were obtained from the Dutch Drug Information Project (GIP). The GIP is a unit of the Dutch Health Care Insurance Board. GIP databases contain data of extramurally prescribed drugs, the statistics refer to 5.6 million persons compulsorily insured in 2000, which is about 55% of all compulsorily insured Dutch.

The total volume of antiepileptic drugs in 1995 was 5.4 DDD per 1,000 insured persons per day in 1995, and increased by 130% to 7.0 DDD per 1,000 insured persons per day in 2001. The larger part of this increase, 60%, was accounted for by the new antiepileptic drugs. Gabapentin, lamotrigine and oxcarbazepine were the most frequently prescribed new antiepileptic drugs. The volume share of new antiepileptic drugs increased from 5% in 1995 to 18% in 2001. The cost of antiepileptic drugs amounted to € 21.5 million in 1995 and rose to € 47 million in 2001; 80% of this increase was due to the introduction of new antiepileptic drugs.

Chapter 2, sub 3 evaluates, in a retrospective follow-up using GIP data, the diffusion process of lamotrigine into daily clinical practice. Understanding the process of diffusion is important in the evaluation of the place in therapy of lamotrigine, its effectiveness in real life and its cost consequences. The study population consisted of a total of 29,718 patients who were prescribed carbamazepine, phenytoin, valproate or lamotrigine for the first time during 1996 - 2000. On average, the market share of lamotrigine was less than 10% of new users. It was found that lamotrigine patients had more frequently used one or more antiepileptic drug prior to the index date when compared to users of one of the conventional antiepileptic drugs (OR 35.5; 95%CI 31.6 – 39.9). In addition, prescribers of lamotrigine were more often neurologists (OR 2.8; 95%CI 2.6 – 3.0) and the prevalence of psychotropic medication was significantly lower (OR 0.35; 95%CI 0.31 – 0.39) with users of lamotrigine than in users of conventional antiepileptic drugs. As time progressed since its introduction in 1995, more patients with characteristics not included in clinical trials started using lamotrigine. The number of patients outside of the age category 18 – 65 increased from 14% in 1997 to 32% in 2000. The number of patients using lamotrigine without prior use of any antiepileptic drug increased from 3% in 1997 to 16% in 2000. Also, the number of patients with off-label use markers in their history increased significantly.

Chapter 2, sub 4 describes a cohort study that used dispensing data from community pharmacies. A total of 1,428 out of 1,586 Dutch pharmacies (90%) received a request in January 2001 to provide anonymous data of all patients to whom lamotrigine was dispensed. The selected pharmacies used one of the three major pharmacy computer systems in the Netherlands. These pharmacies serve an open population of approximately 13 million persons. A total of 1,056 pharmacies (74% response) responded to our request to retrieve the prescription data of all patients to whom lamotrigine had been dispensed. The responding pharmacies covered both large and small pharmacies and both rural and

highly urbanised areas. In all, 3,598 new users of lamotrigine were identified during the observation period. These patients could be followed for a mean observation window of 4.6 years per patient. Baseline characteristics and usage patterns were evaluated for all 3,598 first-time users of lamotrigine. On average, patients were using two other antiepileptic drugs at the start of lamotrigine therapy and approximately 6% of the patients had no history of prior antiepileptic drug use. The discontinuation rate was 25% after one year, and approximately 32% at the end of the 5-year study. Addition of another drug or discontinuation, a global measure of effectiveness, was seen in more than half of the population three years after the start of therapy. The population of randomised controlled trials differed from the study cohort with respect to age, concurrent use of antiepileptic drugs and length of follow-up. This study showed that lamotrigine therapy failed in a considerable number of patients. Furthermore, it showed that data from randomised controlled trials cannot easily be extrapolated to daily clinical practice.

In Chapter 3, four studies are presented concerning the outcomes of lamotrigine in daily clinical practice. These studies were based on a population-based cohort of patients with refractory epilepsy who were recruited via community pharmacists. Chapter 3, sub 1 describes the results of the recruitment procedure. A total of 466 community pharmacists were asked to help with the recruitment of adult patients (n = 1,819) who used lamotrigine. Pharmacists did not inform 183 patients (10%). Of the remaining 1,636 patients, 968 (59%) gave consent; 101 (6%) actively refused, and 567 (35%) did not respond. We found that higher age (HR 1.49, 95% CI 1.22 – 1.81), highly urbanised regions (HR 1.23, 95% CI 1.05 – 1.43), chronic disease scores above six (HR 1.42, 95% CI 1.20 – 1.96) and use of two or more antiepileptic drugs are significantly related to non-consent. Also, addition of another antiepileptic drug and discontinuation of lamotrigine were significantly related to non-consent. Our conclusion is that pharmacy-based recruitment has the potential to reach a broad population, but that selection bias may lead to the misrepresentation of outcome data.

Chapter 3, sub 2 assesses the effectiveness of lamotrigine in a population-based cohort of refractory epilepsy patients and its tolerability in this population. Of the 968 patients who gave their consent for chart review, a sample of 368 patients was selected for the actual review. Effectiveness of lamotrigine therapy was assessed during the first year of use, with patients serving as their own controls. Effectiveness was measured by 1) reduction in seizure frequency and 2) retention time. Effectiveness could only be assessed in 165 patients; assessment in the remaining patients was not possible due to various reasons, such as insufficient medical chart information. Lamotrigine was effective in 40% of the patients who had been prescribed lamotrigine because of insufficient seizure control (n=112), with 14% of these 112 patients becoming seizure free. Lamotrigine was effective in 63% of the patients who received the drug because other antiepileptic drugs were not tolerated (n=53). Logistic regression analysis showed

that several characteristics were significantly associated with effectiveness in the seizure control group. Both longer duration of epilepsy (OR 0.96, 95% CI: 0.94 - 0.99) and higher seizure frequency (OR 0.91, 95% CI: 0.84 - 0.97) were inversely related to lamotrigine effectiveness. The number of antiepileptic drugs used before the start of lamotrigine was significantly correlated to the successful outcome of lamotrigine therapy; the success rate in patients who used one antiepileptic drug previously being at least threefold higher than in patients who used two or more antiepileptic drugs previously. It can be concluded from the present study that lamotrigine is an effective treatment option for patients with varying needs, including those with inadequate seizure control and intolerable side effects.

Chapter 3, sub 3 describes a cost-effectiveness analysis based on the data from the cohort of patients presented in Chapter 3, sub 2. All health outcomes and resource utilisation were recorded for the two-year period, and epilepsy-related direct medical cost was estimated from a health-care perspective. In the analysis, the cost was calculated by multiplying the epilepsy-related resource use of each patient with unit cost. Overall, the total medical cost was € 453 higher in the first year of lamotrigine therapy than in the preceding year. Lamotrigine was effective in 47% of all the patients, making the resultant incremental cost per successfully treated patient € 954 per year.

In Chapter 3, sub 4, data from pharmacy records (Chapter 2, sub 4) and from medical charts (Chapter 3, sub 2) were combined. In this study the validity of electronic pharmacy data was assessed for the criteria discontinuation of lamotrigine, addition of another antiepileptic drug and retention time. For 29 of the 37 (sensitivity 78.4%) patients who discontinued lamotrigine therapy according to the medical record, this event could also be assessed on the basis of pharmacy records. The sensitivity of the addition criterion was 83.3%; in 15 of the 18 patients who had another antiepileptic drug added after start of lamotrigine therapy (noted in the chart record), this event could also be assessed on the basis of pharmacy records. The correlation between the retention time determined from pharmacy records and from medical records was high (Pearson r = 0.91). The conclusion of this study is that pharmacy records are a valid way of measuring the discontinuation, addition and retention time of drugs, and are therefore a valuable tool in pharmacoepidemiology.

Chapter 4 goes into clinical and health-policy decision making in three subchapters. Chapter 4, sub 1 describes the results of a survey held among 490 Dutch neurologists to evaluate the implementation and assessment of the Lamotrigine Prescription Guideline. Of the 232 respondents, only 51 (22%) were familiar with the guideline. Of these 51 neurologists, 80% comply either completely or largely with the guideline. Over 90% of all respondents are in favour of a guideline, preferably developed and evaluated by the medical profession. A majority (58%) of the respondents was positive about taking cost containment measures into consideration in the development of guidelines.

In Chapter 4, sub 2 we present the results of an argumentative policy analysis regarding the Lamotrigine Prescription Guideline. A key feature of this argumentative policy theory is the acknowledgement that different stakeholders may define policy problems quite differently, which may lead to varying and sometimes opposing appreciation of proposed solutions. The results indicate that the problem definitions of policy makers and practising neurologists differed widely, and that the policy measure conflicted with certain professional beliefs. In such cases, the theory of argumentative policy predicts that policy is unlikely to succeed unless policy makers take action to ensure a greater congruence in interpretative frames between themselves and their target population.

In Chapter 4, sub 3 a decision analysis was carried out comparing effectiveness and cost of six treatment strategies comprising carbamazepine, lamotrigine and valproate as first-line and second-line drugs. Three outcome groups were defined: complete success, partial success and failure. Data on seizure control and failure due to adverse effects were derived from literature, cost and quality of life data were obtained from 71 patients. The probability of obtaining complete success varied from 64% (valproate-carbamazepine strategy) to 74% (lamotrigine-valproate strategy). The strategy lamotrigine-valproate was more effective than the least expensive strategy carbamazepine-valproate, but cost more for each additional effectively treated patient. Subsequent analysis showed that changing the inclusion criteria used in the selection of the studies from the literature had an important effect on cost-effectiveness ratios of the various strategies. The conclusion from the decision analysis is that lamotrigine first-line strategies did not prove to be cost-effective. However, lamotrigine second-line strategies can be cost-effective depending on the willingness to pay for patient improvement.

The general discussion (Chapter 5) aims at putting the individual studies regarding the value assessment of lamotrigine into a broader perspective. There is still a high degree of uncertainty about the value of a drug for daily clinical practice at the moment of drug approval, this is due mainly to the well known and accepted limitations of drug evaluation before approval, such as the relatively small, selected study populations and the limited study duration. Observational studies, either with target data collection or administrative databases, may provide additional information about the safety, effectiveness and cost-effectiveness of a new drug in daily practice. A staged approach for this way of value assessment is presented in the final paragraph of this chapter.

SAMENVATTING

In dit proefschrift staat de waardebepaling van het nieuwe anti-epilepticum lamotrigine in de klinische praktijk centraal. Epilepsie is één van de frequentst voorkomende neurologische ziektebeelden, de incidentie in westerse landen wordt geschat op circa 50 patiënten per 100.0000 inwoners. Het is een aandoening die ontstaat door spontane, plotselinge en kortdurende overmatige ontladingen van hersencellen, die functiestoornissen veroorzaken afhankelijk van het hersengedeelte waar deze cellen zich bevinden. De behandeling van epilepsie berust voornamelijk op het onderdrukken van de aanvallen door medicamenteuze interventie met anti-epileptica. De meest gebruikte anti-epileptica zijn al meer dan 30 jaar beschikbaar, deze geneesmiddelen onderdrukken de aanvalsfrequentie bij de meeste patiënten goed. Toch is bij 30-40% van de patiënten het behandelingsresultaat onvoldoende; de patiënt wordt niet aanvalsvrij of heeft onacceptabele bijwerkingen. Daarnaast worden de oudere anti-epileptica gekenmerkt door een groot interactiepotentieel en door een verhoogde kans op vruchtbeschadiging. De komst van lamotrigine, in 1995, heeft het aantal behandelstrategieën voor patiënten met epilepsie vergroot. Het geneesmiddel kwam echter niet direct voor vergoeding door zorgverzekeraars in aanmerking. Redenen hiervoor waren de hogere kostprijs van lamotrigine en onvoldoende duidelijkheid omtrent de meerwaarde van lamotrigine ten opzichte van de oudere anti-epileptica. In 1997 doorbreekt het College voor zorgverzekeringen (CVZ) de vergoedingsimpasse. Het College voor zorgverzekeringen stelt het protocol 'Gebruik Lamotrigine' op, met als doelstelling het gebruik te beperken tot die situaties waarin lamotrigine een therapeutische meerwaarde bezit. Essentie van het protocol is dat lamotrigine pas overwogen dient te worden wanneer de mogelijkheden van behandeling met bestaande middelen optimaal benut zijn. Niet eerder zijn in Nederland via een protocol nadere voorwaarden gesteld aan de aanspraak op een geneesmiddel.

Hoofdstuk 1 is een algemene inleiding waarin nader wordt ingegaan op het ziektebeeld epilepsie en de behandeling hiervan. Ook worden de vier fasen voor de waardebepaling van een geneesmiddel geïntroduceerd: werkzaamheid, toegankelijkheid, effectiviteit en doelmatigheid. Gegevens omtrent de werkzaamheid van een geneesmiddel worden verzameld in gerandomiseerde klinische onderzoeken in strikt geselecteerde patiëntpopulaties. Direct na registratie van een nieuw geneesmiddel is er dan veelal nog weinig bekend van de effectiviteit en veiligheid in de dagelijkse praktijk, een situatie waarin het geneesmiddel ook aan andere patiëntpopulaties wordt voorgeschreven. Observationeel, farmacoepidemiologisch onderzoek is geschikt om de waarde van een geneesmiddel in de dagelijkse praktijk nader te bestuderen. Dit proefschrift bundelt een aantal observationele onderzoeken naar de waarde van lamotrigine in de dagelijkse praktijk.

Hoofdstuk 2 beschrijft de plaatsbepaling van de nieuwe anti-epileptica en in het bijzonder die van lamotrigine. Hoofdstuk 2.1 is een literatuuronderzoek over de nieuwe anti-epileptica. Hun werkingsmechanismen, werkzaamheid, effectiviteit, bijwerkingenprofiel en farmacokinetiek worden beschreven en diverse keuzecriteria worden aangereikt.

In hoofdstuk 2.2 staan de volume- en kostenontwikkeling van anti-epileptica in Nederland centraal. Om het gebruik van anti-epileptica te onderzoeken zijn gegevens ontleend aan het Geneesmiddel Informatie Project (GIP) van alle in de periode 1995 – 2001 afgeleverde anti-epileptica. Het aantal Defined Daily Doses (DDD) per 1000 verzekerden per dag stijgt met 130% van 5,3 DDD per 1000 verzekerden per dag in 1995 naar 7,0 in 2001. De nieuwe anti-epileptica dragen voor 60% bij aan deze stijging. Hun aandeel stijgt van 0,27 DDD per 1000 verzekerden per dag (5%) in 1995 naar 1,2 DDD per 1000 verzekerden per dag (17,5%) in 2001. Gabapentine, lamotrigine en oxcarbazepine zijn de meest voorgeschreven nieuwe anti-epileptica.

In 1995 bedragen de totale kosten van farmaceutische zorg voor anti-epileptica € 21,5 miljoen. De bijdrage van de conventionele anti-epileptica is in dat jaar € 17,8 miljoen (83%). In 2001 zijn de totale kosten meer dan verdubbeld en wordt € 47 miljoen uitgegeven aan farmaceutische zorg. Met name de introductie van nieuwe anti-epileptica heeft geleid tot deze kostenstijging. Van de totale kostenstijging komt 80% op rekening van de nieuwe anti-epileptica. Hiermee stijgt het marktaandeel van de nieuwe antiepileptica van € 3,8 miljoen (17%) in 1995 naar € 24,2 miljoen (52%) in 2001.

In hoofdstuk 2.3 staat het verspreidingsproces (diffusie) van lamotrigine in de dagelijkse praktijk beschreven. In dit onderzoek wordt gebruik gemaakt van de GIP gegevens van 29.718 patiënten die lamotrigine of één van de oudere anti-epileptica carbamazepine, fenytoïne of valproïnezuur gebruiken. Centraal staat hoeveel patiënten met lamotrigine starten en hoe hun karakteristieken verschillen van die van patiënten die met de oudere anti-epileptica starten. Het marktaandeel van lamotrigine is gemiddeld minder dan 10% en daarmee beduidend lager dan dat van carbamazepine of valproïnezuur. In vergelijking met de oudere anti-epileptica wordt lamotrigine vaker voorgeschreven aan patiënten met een historie van andere anti-epileptica (OR 35,5; 95%CI 31,6 – 39,9) en door neurologen (OR 2,8; 95%CI 2,6 – 3,0). Patiënten die met lamotrigine starten hebben minder vaak psychotropica gebruikt dan patiënten die met de oudere anti-epileptica starten (OR 0,35; 95%CI 0,31 – 0,39). Naarmate er meer tijd na de introductie van lamotrigine verstrijkt wordt lamotrigine meer voorgeschreven aan patiëntpopulaties die niet in de registratieonderzoeken zijn geïncludeerd. Het aandeel patiënten buiten de leeftijdscategorie 18-65 jaar stijgt van 14% in 1997 naar 32% in 2000. Het aantal patiënten dat lamotrigine als eerste anti-epilepticum krijgt voorgeschreven stijgt van 3% in 1997 naar 16% in 2000. Ook worden er in de loop van de tijd meer psychotropica in de voorgeschiedenis van patiënten die met lamotrigine

starten gezien; dit zou kunnen duiden op een toenemend gebruik van lamotrigine voor andere indicaties dan epilepsie.

In hoofdstuk 2.4 worden gegevens van een landelijk cohort lamotrigine gebruikers beschreven. In dit hoofdstuk staan de wijze van gegevensverzameling en de patiëntkarakteristieken centraal. Geanonimiseerde prescriptiegegevens van 1.056 openbare apotheken in Nederland zijn gebruikt om een cohort van 3.598 patiënten die starten met lamotrigine te beschrijven. De karakteristieken van het landelijke cohort verschillen, qua leeftijd, medicatiehistorie en duur van follow-up, met die van de patiënten die geïncludeerd zijn in de registratieonderzoeken. In dit onderzoek wordt de retentietijd van lamotrigine als een grove maat voor de effectiviteit van dit geneesmiddel beschouwd. De retentietijdanalyse laat zien dat na een jaar 25% van de patiënten met lamotrigine is gestopt en na drie jaar follow-up 32%. Na drie jaar follow-up is bij meer dan de helft van de patiënten lamotrigine gestopt of is er een ander anti-epilepticum toegevoegd aan de therapie.

De effectiviteit van lamotrigine in de dagelijkse praktijk wordt in hoofdstuk 3 beschreven. De onderzoeken in hoofdstuk 3 zijn gebaseerd op een landelijk cohort van patiënten met refractaire epilepsie. Hoofdstuk 3.1 beschrijft hoe de patiënten voor het onderzoek gerekruteerd zijn. In totaal zijn 466 openbare apotheken verzocht om 1.819 lamotrigine gebruikende patiënten aan te schrijven met het verzoek mee te doen met het statusonderzoek. In 183 gevallen heeft de openbare apotheker besloten het verzoek niet door te sturen. Van de resterende patiënten hebben 968 patiënten met het verzoek ingestemd (59%), 101 patiënten weigeren deelname aan het onderzoek (6%) en 567 patiënten hebben nooit gereageerd op het verzoek (35%). Uit de analyse van karakteristieken van de verschillende responsgroepen blijkt dat hogere leeftijd (HR 1,49, 95% CI 1,22 – 1,81), het wonen in stedelijke regio's (HR 1,23, 95% CI 1,05 – 1,43), een chronische ziektescore hoger dan zes (HR 1,42, 95% CI 1,20 – 1,96) en het gebruik van twee of meer anti-epileptica in de voorgeschiedenis gerelateerd zijn aan het niet verlenen van toestemming aan het onderzoek. Ook het stoppen van lamotrigine of het toevoegen van een ander anti-epilepticum zijn gerelateerd aan het niet verlenen van toestemming. De conclusie is dat via openbare apotheken een brede patiëntenpopulatie wordt bereikt, echter door het optreden van selectiebias kan vertekening van de uitkomstgegevens optreden.

In hoofdstuk 3.2 wordt een retrospectief follow-up onderzoek gepresenteerd. Bij 368 patiënten zijn de statusgegevens geanalyseerd om een beeld te krijgen van de effectiviteit van lamotrigine bij patiënten met refractaire epilepsie. De effectiviteit van lamotrigine is bestudeerd gedurende het eerste jaar van gebruik, patiënten dienden hierbij als hun eigen controle. De effectiviteit van de lamotriginebehandeling is bepaald aan de hand van 1) reductie in de aanvalsfrequentie en 2) de retentietijd van lamotrigine. Door diverse redenen, waaronder de beperkte hoeveelheid informatie in

diverse medische dossiers, zijn uiteindelijk de gegevens van 165 patiënten geanalyseerd. Lamotrigine is effectief bij 40% van de patiënten die het geneesmiddel kregen vanwege onvoldoende aanvalscontrole met andere anti-epileptica (n=112) en 14% van deze 112 patiënten werd aanvalsvrij gedurende het eerste jaar van behandeling met lamotrigine. Lamotrigine is effectief bij 63% van de patiënten die het geneesmiddel kregen vanwege onacceptabele bijwerkingen van andere anti-epileptica (n=53). De uitkomst van de behandeling van lamotrigine is, bij de onvoldoende aanvalscontrole groep, gerelateerd aan bepaalde patiëntkenmerken. Zowel een langere ziektegeschiedenis van epilepsie (OR 0,96, 95% CI: 0,94 – 0,99) en een hogere aanvalsfrequentie (OR 0,91, 95% CI: 0,84 – 0,97) zijn negatief gerelateerd aan de effectiviteit van lamotrigine. Het aantal anti-epileptica in de voorgeschiedenis is eveneens gerelateerd aan een succesvolle behandeling met lamotrigine; patiënten met slechts één anti-epilepticum in de voorgeschiedenis hebben een drie keer hogere kans op een effectieve behandeling met lamotrigine dan patiënten met drie anti-epileptica in hun voorgeschiedenis. Geconcludeerd wordt dat lamotrigine een anti-epilepticum is met een toegevoegde waarde bij patiënten met onvoldoende aanvalscontrole en bij patiënten met onacceptabele bijwerkingen op andere anti-epileptica.

Hoofdstuk 3.3 beschrijft een kosteneffectiviteitanalyse op basis van de gegevens van het patiëntencohort gepresenteerd in hoofdstuk 3.2. In dit hoofdstuk worden de directe medische kosten berekend in het jaar voor en na start van lamotrigine en gerelateerd aan de effectiviteit van lamotrigine. In het eerste jaar na de start van lamotrigine nemen de totale medische kosten toe met € 453. Lamotrigine is bij 47% van de patiënten effectief, dit resulteert in een incrementele kosteneffectiviteit ratio van € 954 per effectief behandelde patiënt per jaar.

Hoofdstuk 3.4 is een validatiestudie, hierin worden de prescriptiegegevens uit hoofdstuk 2.4 gekoppeld aan de statusgegevens uit hoofdstuk 3.2. De validiteit van de farmacoepidemiologische parameters van stoppen, add-on en retentietijd zijn in dit hoofdstuk geanalyseerd. Bij 29 van de 37 (sensitiviteit 78.4%) patiënten die stoppen met lamotrigine volgens de informatie in de medische status wordt dit ook geconcludeerd op basis van de analyse van de prescriptiegegevens. De sensitiviteit van de add-on parameter is 83.3%, bij 15 van de 18 patiënten die een ander anti-epilepticum toegevoegd krijgen na de start van lamotrigine (volgens de statusgegevens) wordt dit ook geconcludeerd op basis van een analyse van de prescriptiegegevens. Er is een goede correlatie tussen de retentietijd bepaald op basis van de prescriptiegegevens en de retentietijd bepaald uit de statusgegevens (Pearson r = 0.91). De conclusie is dat prescriptiegegevens een valide bron zijn om stoppen, toevoegen en retentietijd van geneesmiddelen te bepalen.

Hoofdstuk 4 behandelt diverse aspecten van de klinische en gezondheidseconomische besliskunde. Hoofdstuk 4.1 beschrijft de resultaten van een vragenlijst gericht op de bekendheid van het College voor zorgverzekeringen (CVZ) protocol 'Gebruik Lamotrigine' onder de doelgroep van neurologen. De vragenlijst is gestuurd aan 490 neurologen en de vragenlijst is door 232 neurologen geretourneerd. Slechts 51 neurologen waren bekend met het protocol 'Gebruik Lamotrigine' en hiervan gaf 80% aan de strekking van het protocol te volgen. De noodzaak van een epilepsierichtlijn wordt door meer dan 90% van alle respondenten onderschreven. Zij spreken de voorkeur uit dat een dergelijke richtlijn wordt opgesteld en geëvalueerd door de beroepsgroep. In meerderheid (58%) zijn de respondenten positief over het opnemen van maatregelen betreffende kostenbeheersing in een dergelijk protocol.

Hoofdstuk 4.2 gaat nader in op de onbekendheid van het protocol 'Gebruik Lamotrigine' onder de beroepsgroep. In dit hoofdstuk worden de resultaten van een argumentatieve beleidsanalyse gepresenteerd aangaande het protocol. Kern van de argumentatieve beleidsanalyse is dat de kans op de gewenste gedragsverandering niet alleen bepaald wordt door de keuze en de kwaliteit van de inzet van een beleidsinstrument (het protocol 'Gebruik Lamotrigine'), maar ook door de mate waarin de gevraagde handelswijze zinvol is in de ogen van de doelgroep, dat wil zeggen binnen de handelingstheorie van de doelgroep. De resultaten van onze analyse laten zien dat de beleidsmakers en neurologen vanuit een geheel andere, soms tegenovergestelde, invalshoek onderwerpen zoals de inzet van nieuwe anti-epileptica benaderen. Dit geeft aan dat de inzet van het protocol als beleidslijn weinig kans tot slagen heeft en dat beleidsmakers actiever moeten trachten hun handelingstheorie te laten overlappen met de handelingstheorie van de doelgroep.

Hoofdstuk 4.3 beschrijft een economische beslismodel naar de effectiviteit en de behandelkosten van zes verschillende behandelopties voor nieuwe patiënten met epilepsie. Modelleren in kosteneffectiviteitsonderzoek heeft tot doel gegevens uit verschillende bronnen bijeen te brengen. In dit model wordt de effectiviteit van de verschillende behandelopties gebaseerd op literatuurgegevens; de kosten worden gebaseerd op de gegevens uit de kostendagboeken van 71 patiënten met epilepsie. In het model worden behandelopties van carbamazepine, lamotrigine en valproïnezuur met elkaar vergeleken. De effectiviteit (aantal aanvalsvrije patiënten) varieerde van 64% (valproïnezuur-carbamazepine strategie) tot 74% (lamotrigine- valproïnezuur strategie). De lamotrigine-valproïnezuur was effectiever dan de goedkoopste strategie carbamazepine-valproïnezuur, maar tegen zeer aanzienlijke extra kosten per extra effectief behandelde patiënt. Uit nadere analyses blijkt dat het model sterk kan worden beïnvloed door de beschikbare literatuurgegevens omtrent de effectiviteit van de diverse behandelopties. De conclusie uit het beslismodel is dat er geen aanwijzingen zijn die de doelmatigheid van lamotrigine als middel van eerste keuze onderschrijven.

Hoofdstuk 5 tracht de bevindingen van de individuele hoofdstukken aangaande de waardebepaling van lamotrigine in een breder perspectief te plaatsen. Er is een toenemende behoefte om de waarde van een geneesmiddel na de introductie in de dagelijkse praktijk goed te evalueren. Observationele onderzoeken, gebruikmakende van prescriptiedatabases of van statusgegevens kunnen een bijdrage leveren aan de kennis omtrent de effectiviteit, de veiligheid en de doelmatigheid van een nieuw geneesmiddel. In de afsluitende paragraaf van hoofdstuk 5 wordt hiertoe een aanzet gegeven.

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[1] Arthur Japin. Een schitterend gebrek. Uitgeverij De Arbeiderspers, 2004.

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Pieter Knoester studied pharmacy at Utrecht University, where he obtained his degree in 1994. He trained as a hospital pharmacist at Haarlem Hospital Pharmacy under hospital pharmacist Ruud van der Hoeven.

In December 1999 he started his PhD research at the Department of Clinical Pharmacy at Nijmegen Medical Centre under hospital pharmacist Remco de Jong. Since January 2003 he has been hospital pharmacist at the Department of Pharmacy of Erasmus Medical Centre Rotterdam, which is headed by Dr Peter Roos.

Pieter Knoester is married to Martine Uiterwijk Winkel. They are the proud parents of Maarten and Julius, and are expecting a third "child in time", who is planned to arrive early 2006.